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THE NATURE OF CLINICAL MEDICINE*

F. M. R. WALSHE

London, England

My first task is to express to the President of the University and to the Faculty of the School of Medicine my deep sense of the honor of this invitation to give the Thayer Lectures.

It so happens that I was privileged to meet Dr. Thayer on two separate visits to this hospital. First in 1910 when a young graduate I made ward rounds with him, and later in 1925 when on a longer visit to Baltimore I renewed my acquaintance and captured once more the sense of being in the presence of a humanist physician, a man who bore the authentic note of the clinical tradition that made this school of medicine famous.

In this somewhat disillusioned age, the cynic loves to tell us that the idea that we may draw strength and inspiration from the examples of our predecessors in medicine is an idle fancy and a form of ancestor worship. Yet medicine is rooted in its past, and of this past its great men were the builders, and they should command the reverence of all who enjoy the fruits of their labors and example, as we do enjoy them.

It is with this thought in mind that I approach this lecture. Many of my predecessors in this lectureship have discoursed upon the advances in medical knowledge which this age has seen in such abundance; advances which the lecturers themselves have done so much to achieve. Yet there is more in medicine than discovery and technical triumphs. We are a learned profession with the moral and intellectual responsibilities of a profession. The remembrance of Dr. Thayer surely offers a clear invitation to consider this aspect of medicine. Therefore I shall not attempt this afternoon to lay before you the chart of some new-found field of discovery, but I shall invite you to stand back with me from the manifold details of our work, to view medicine as a whole, to seek to place it in the scheme of humane and natural knowledge, and in the framework of our lives. For medicine is more than the sum of the empirical arts and the applied sciences that we employ for the preservation and for the restoration of the health of our fellow men. It is a way of life that demands of us speculative and practical wisdom as well as knowledge.

Each of us hopes to be something more than an ingenious physician or a skillful surgeon. The account of the Creation in the Book of Genesis closes with these words, 'God ended the work which he had made, and behold it was very good.'

* Lecture I of the eighteenth course of lectures under the William Sydney Thayer and Susan Read Thayer Lectureship in Clinical Medicine. Delivered at The Johns Hopkins Hospital, May 21, 1952.

This, I venture to believe, is how each one of us as he approaches the end of his work as a doctor would wish to feel, in retrospect, about it: that it was 'very good'. There is also, of course, the Greek sense of 'the good life'; a secular ideal with its own intrinsic virtues. Choose which you will, the life in medicine may be good, if our conception of medicine is as comprehensive as it should be.

I therefore crave your indulgence for what I shall say of the nature of medicine.

In brief, and to anticipate my thesis, let me say that my submission is that while medicine has a place as of right within the body of the natural sciences, yet it transcends these and has in it elements of Humanism and of History.

Thus, Humanism, Natural Science and History are the elements out of which medicine, worthily conceived, may be integrated into a harmonious whole.

Let us first consider the intellectual structure of medicine in its relation to natural science. As you know, it is common for this theme to be expounded in terms of two antitheses: namely, art and science, observation and experiment, and we are apt to think of these aspects as distinct and separable. Yet, experiment is merely one mode of observation, and while it may be possible to think of art without science, I submit that a science must be an art—and this for reasons that I shall hope to give you. We should be wrong, therefore, to divide up our notion of the intellectual structure of medicine into separate components in this fashion. Classification at best is a static category, and one that needs to be illuminated by the idea of process if it is not to cramp thinking. Thus, the concept of evolution is essentially the statement in temporal and dynamic terms of the static classification of the animal kingdom. In other words, classification and evolution are two languages about a single set of events, the full understanding of which requires them both.

Some have maintained, though it is not an educated view, that medicine has no proper status as a scientific discipline, and that it is no more than applied physiology, chemistry and physics. And the reason they give is that medicine does not carry its analysis of phenomena back to fundamental notions but stops at arbitrarily chosen half-way houses where it meets and tends increasingly to borrow from the other sciences, and is thus merely a derivative discipline.

But surely, in this regard medicine is no exception amongst the biological sciences. Physiology itself has been persistently borrowing from the other sciences until in the process it has become a collection of applied sciences, and has in some aspects almost ceased to retain its prime function, which is the discernment and rational formulation of the dynamic properties of organisms. In fact, we might trace all the sciences back through physics to mathematics, and deny independent status to all but mathematics. Here, too, philosophy might then step in and claim a subordinate status for mathematics.

The fact is that every scientific approach to the analysis of nature, living and dead, stops at a halfway house when tracing its ideas back to their foundations,

and is content with generalities sufficient for its immediate purpose. Natural science is concerned with proximate causes. First causes are the province of philosophy. Medicine, therefore, stands on the same footing as any other branch of the biological sciences.

If this be granted, we may proceed to consider shortly what is embodied in the terms observation and experiment. And I begin with one of Whitehead's aphorisms, namely, that observation is selection. It is a process of discrimination that selects and discards from the sum total of presenting sensory data. This is to say that the notion of importance enters into it, and this notion can arise only from antecedent experiences. A naturalist has written, 'we see clearly only what we know thoroughly'. In other words the process of observation is bound up with the entertainment of ideas and with a sense of what is important in any given instance.

Observation is further conditioned, as it were, by its interpretation in terms of concepts. The idea that there is any activity of the mind that corresponds to the conception of pure reason is an illusion. The mind has no such function. All processes of reason are influenced by and moulded by feeling. Reason never works in an emotional vacuum.

Perhaps nowhere is this complex quality of observation more immediately evident than in clinical medicine. The experiences we encounter in the clinic and at the bedside are random and not predetermined by us. We cannot repeat them at will, and they may have upon occasion a maddening ambiguity. The trained clinical observer constantly scans the changing flux of phenomena, looking for the familiar pattern or sequence that will give it meaning, and filling in the gaps out of earlier experiences. When the pointers he seeks do not lie open to the observing senses, then he uses some formal test to reveal them, and in so doing he passes the vague frontier that separates plain observation from experiment.

The very term 'clinical examination' indicates that we are picking and choosing according to notions already entertained.

It is only the exceptional mind that carries this discriminating process into the unfamiliar and grasps new patterns, from which he may forge new generalizations.

Thus observation is not quite the dispassionate recording of all presenting phenomena that we may have thought it to be. It is not a coldly rational process at all, but something more than this.

What, then, is to be said of experiment? In part the answer is simple, in that the mind that observes is the same that devises, performs and interprets experimental procedures. There is not some higher order of reasoning attaching to experimental observation, and indeed, what I shall have to say in my next lecture will, I believe indicate, how poor may be the level of reasoning that sometimes goes to the interpretation of experiment.

A simple analogy may give us a clue to the essential distinction between simple observation and experiment, as when we speak of observation as the examination of nature, and of experiment as the cross-examination of nature; the forcing it to give answers that it does not spontaneously yield. Bacon spoke of this process as 'putting nature to the question'.

Now whether we observe the phenomena that nature presents, by the trained senses, or whether we make experiments, we are bound by the same necessity. The processes we study have to be translated into a language, a grammar of science, and they have to be sorted, interpreted and finally made to emerge as clearly formulated propositions, as exemplifications of what we call the laws of nature. Thus we need a precise terminology logically used if we are to bring intellectual light to bear upon phenomena.

Now the aim of the scientific observer is to grasp the principles inherent in the stream of evanescent phenomena. He has to sum up unordered data in general terms that are independent of the particular embodiments before him.

The aim of experiment is to force this end when simple observation cannot do so. The experimenter, guided by ideas already in his mind, standardizes conditions or sets up an apparatus that will make possible the analysis of a complex process into its components, free from complicating factors. This is what Whitehead calls 'cooking the facts for the sake of exemplifying the law'.

Experiment thus provides a double clarification: the formulation of a law, and the exemplification of it in as simple and uncomplicated a medium as possible.

Now it is clear that this method may involve a greater degree of abstraction than simple observation, for many more facts out of the total presenting are deliberately excluded from operation, and this creates the great danger of the experimental method and lends it a measure of artificiality. For in nature nothing is isolated and every activity depends upon, and is influenced by its environment of process and of structure. In other words the abstractions derived from the experimental method may be vitiated by what they leave out of account.

This tendency may lead to a narrowing of the mind and is adverse, perhaps, to a free play of ideas over the sum of presenting phenomena.

This brief summary indicates the complex of mental operations that issue in and arise from observation and experiment, and show us that the observational and conceptual orders of experience are inseparably mixed.

We see this mixture in Harvey's work on the circulation of the blood, for it was observation utilizing the method of experiment, but determined by a theory of Aristotle's and a close knowledge of Galen's work, that led him to revise Galen's theory of the circulation. Yet in discarding Galen's theory about the existence of pores in the heart in favor of his own view that there were communications between arteries and veins, Harvey was not recording an experi-

mental datum, he was speculating, for the communications in question were not revealed until after his day.

Thus we do William Harvey less than full justice when we honor him for introducing the method of animal experiment into medicine. We owe him more than this, namely the lesson that both simple and experimental observation are inseparable from the active entertainment of ideas and the courage to speculate logically.

It is perhaps necessary in our day to emphasize this, when so many original observers seem content to place facts on record in ever increasing number, forgetting that the natural rhythm of healthy scientific thought is one of observation and synthesis, and that facts are no more than data for rational study.

Let us now turn to the second pair of antitheses in terms of which medicine is so often considered; namely, art and science. Here, even more than in the case of observation and experiment, we need precise definitions.

When we speak of the art or the arts of medicine we generally refer to the practical arts; that is, procedures traditional in origin and in form, which embody the common-sense experience of the generations, are governed by no formulated laws and exemplify no general principles. These predominated in medicine even so comparatively recently as in my own student days, but the applications of science are progressively replacing them, and these applications are determined by ideas inductively derived and possessing some measure of rational basis. There is a natural tendency for practical arts to be converted into applied science, for even these arts are based on rules, and rules are in fact general propositions applicable to particular situations. Thus general ideas emerge from activities, and then rationalize and modify them.

I have used the term common-sense knowledge, and perhaps I may say a word about the relation of this to what we call scientific knowledge. It would be wrong to suppose that common sense knowledge has a lower value as truth than scientific knowledge. The difference is that in the two cases the knowledge exists in the mind in different modes. Before we can know anything with a scientific or perfect knowledge, that is by its proximate causes and the principles it exemplifies, we know it imperfectly by the knowledge of everyday life and experience. No one can have a universal scientific knowledge, and most of what we know we know simply by the light of common sense: that is by the evidence of the senses and by the spontaneous arising in the mind of certain self-evident principles: such as that the whole is greater than the part, that a thing cannot both be and not be, and so on. This order of knowledge expresses the natural sense of the intellect, and may be as valid as scientific knowledge, but while we may know things infallibly by common sense we do not always know their causes or how we come to know them. Therefore, we may not despise common sense, for in medicine we cannot do without it in the present imperfect state of

scientific knowledge. I doubt if we shall ever be able to do without it, though some scientifically-obsessed physicians endeavor to do so with results to their patients often horrid to dwell upon.

But the practical arts do not exhaust this question of art in medicine. Here we turn from the concrete to the abstract, and the problem becomes not that of art *and* science, but that of art *in* science.

Let us consider the essential intellectual methods by which, as clinicians we must work. Our aim is to transform the confused and often ambiguous data of experience into the clearly formulated propositions of a rational body of knowledge, and also, as doctors faced by our patients, to identify their situations as particular examples of the general principles of such a body of knowledge.

The way in which we do this is a special example of what in the middle ages were known as the liberal arts, namely, grammar, rhetoric and logic: rhetoric being here understood not as the sophistries of the politician or the advocate, but as the use of analogy and metaphor.

For the trained observer every complex of presenting phenomena is a text to be read, translated into a grammar of science, rhetorically expanded and logically interpreted. Thus in diagnosis the signs and synptoms are noted and translated into a technical language which comes to stand for them, and the terms of this language—or grammar—are built into statements.

In this way a verbal classification ensues: signs and symptoms are grouped into patterns and sequences and their time-space relationships are clarified. From these patterns and sequences we seek to discover the future course of events: this is prognosis. In other words from the verbal statements about the beginning and the middle of the story of the illness we seek to formulate its probable end.

But there are yet further terms in which our original data have to be discussed: we have to think of the data in terms of departure from normal function, this is the physiological analysis: in terms of reaction to exogenous or endogenous noxa, this is the pathological analysis, and then in terms of causation, that is the etiological analysis.

These different analyses are seen to be different fields of discourse about a single set of events, and this diversity of discourses constitutes what used to be known as the rhetorical expansion of the subject. Finally, we face the logical interpretation and synthesis of the data, so that these may emerge as rational propositions of science, as exemplified in the particular case under study.

No one would deny that this is the method of natural science, and equally no one would deny that this complex intellectual operation demands gifts of insight, the ability to detect analogies, patterns and characteristics sequences, and the capacity for logical interpretation. These gifts are the intellectual arts, and they are an integral element in scientific thought at its best,

and in whatever field of knowledge they are exercised. It is of all this I speak of when I refer to art in science.

Thus, in virtue of its use of this method, clinical medicine can rightly claim its place in the body of the natural sciences.

We come to consider the other elements that enter into medicine, comprehensively understood, namely, history and humanism.

Let me first take history. What I shall have to say thereon may appear strange and unacceptable to you, yet a fresh point of view is always worth entertainment even if we end by rejecting it.

My submission is that there is in the clinical study of illness a first step which does not rightly belong to the natural sciences, but to historical science. This step is the taking of the history. When we do this we seek to obtain a record of past events that have not happened under our observation, that for us have never been sense data: events we cannot always, or even commonly, submit to control and verification by scientific methods as these are usually understood.

This record of the past we subject to a process of critical thought. From its sum we select and discard, and assemble what we think relevant in the light of our past experience of the method. The final product of this process is the sublimation of a certain kind of evidence from one source and a critical study of it from another.

Further, since this evidence from the past is not merely a matter of events but, in part at least of human actions, a new element not encountered in natural science makes its appearance.

I am suggesting that between an event and a human action a distinction has to be drawn. What we call the 'history' in medicine is not a mere chronicle of events, but is a true exercise in historical method as I shall proceed to define this.

Let me review: the true method of natural science is the observation of events, the flux of which forms a moving spectacle before us, with such verifications and repetitions of this observation as sound conclusions may require. Having observed these events as particulars, we then proceed to determine the patterns and sequences into which they fall, and from these we go on to make those generalizations that are known as laws of nature.

The historian, on the other hand, is not concerned with events which he perceives, nor does he seek to make abstractions and generalizations, nor does he predict—in this last point being singularly removed from the natural scientist in his aims.

He is concerned with human actions that lie in the past, though they have their consequences, perhaps, in the present. These actions are not the sense data of natural science, and the historian's evidence is the written and archaeological records, to which he applies a critical judgment based on experience,

using those processes of selection and assembly that are the essence of true clinical history taking.

The historian's real quest is to uncover the motive forces of these human actions, and not merely to record them, for this last is chronicling only. Events for him are not spectacles which he observes and seeks to classify, but something he seeks to go behind so that he may discern the human thoughts and motives, conscious and unconscious, that they express.

An English historian, Collingwood, draws this distinction between historian and natural scientist in these words: 'When a scientist asks 'why did that piece of litmus paper turn pink?', he means, 'on what occasions do pieces of litmus paper turn pink?' When a historian asks 'why did Brutus stab Caesar?, he means 'what did Brutus think which made him decide to stab Caesar?' For him the cause of the event means the thought in the mind of the person by whose agency the event came about. Collingwood speaks of this as 'the inside of the event'. It is the role of the natural scientist to ask the first kind of question, and that of the historian to ask the second kind, and we see that they are two very different kinds of question. The answer to the historian's question does not lead to the formulation of general principles nor to predictions. They cannot so lead.

Now what is the relevance of all this to medicine? Clearly there are states of illness in which human action plays no determining part in the sense of thought or motive, but when we come to what it is now the fashion to call psychosomatic medicine and to psychological medicine, we see at once the relevance of the matter, and the question arises whether psychological medicine belongs to the natural sciences or to historical science—two different disciplines.

In fact, let me say at once what I am proposing. It is that medical psychology, or psychological medicine or psychiatry—whatever you prefer to call it—or rather I should say 'them' for there are many psychiatries—is a discipline belonging to history and not to natural science.

Since the eighteenth century, what our ancestors called the science of human nature has assiduously sought to establish itself as a discipline within the body of the natural sciences.

A respected authority, the English psychiatrist Bernard Hart, a generation ago argued that the data of the psychiatrist are strictly comparable with those of the natural scientist, and that a scientific concept in psychiatry 'must explain the observed facts, and these must be capable of verification by repeated reference to experience and experiment'.

Yet what concept in psychiatry conforms to these postulates? Surely few and these only fortuitously. Am I mistaken in supposing that the aim of psychiatry is the discerning and unravelling of the mental processes, conscious and unconscious, that lie behind the 'observed facts'; and are not these ob-

served facts the consequence of past thoughts and actions that the psychiatrist can neither observe nor verify by repetition? The essential data here are the mental processes behind the facade of the observed facts. Hart adds that psychiatry belongs to biology, and like it shows the quality of 'purpose' in the material considered. But the purpose of biology is teleology and not the purpose that underlies human actions. Here is a simple confusion of words.

Now I am well aware that clinical psychology is a very different affair from much experimental psychology, and that a great deal of the latter does belong to natural science. But it is not my fault if psychologists use the same term for different thoughts and activities—this terrible carelessness in the use of what should be a precise terminology is not peculiar to psychology, though it is seen nowhere else in such abundance, or productive of such confusion of thought and expression.

It is odd that no one but the historian Collingwood should have seen this close relation of clinical psychology to history, and its remoteness from natural science, both in its methods and in its aims.

Yet, surely, the fact is that the psychologist in medicine is not primarily concerned with events, nor does he use the sense data that are the necessary data of natural science, or at least that he does not use them in the same way. His primary concern is the application of the historical method to the fragmentary and often obscure records of human thought and action. It is upon this application that all depends.

The springs of human action that are his quest are not data of observation, open to inspection, to control or to repetition. It is only by reliving in his own mind these long past activities—as revealed by historical inquiry, and in the context of his own experience of the method, that he can understand the mental activities underlying the concrete situation he is studying. The psychologist's problem is a concrete one, and does not lead to the formulation of universals or predictions, for there is no universal blue print to the springs of human thoughts and actions applicable to all persons at all times.

I submit, therefore, that the endeavor of two centuries to fit psychology within the realm of the natural sciences is based on a false analogy, to which the term 'human nature' lends color. This analogy has impeded the growth of a medical psychology under the aegis of historical science.

Whenever I have put this view forward, my psychiatric colleagues have become very explosive, as though I was seeking to degrade their art. But it is not a degradation to place a discipline where it seems to belong, and to remove it from a field of knowledge that has different methods and different aims. Only confusion can come from a failure to consider this very cogent question, and we shall certainly not answer it until we have asked it. It is a question to be both asked and answered.

I submit, then, that there is in medicine an historical element that is not part of natural science as this is generally understood, for it does not fulfill the postulates of natural science.

I come finally to Humanism. Here is the element that lifts medicine above both natural and historical science, and makes of it something greater than either.

Humanism is a term sadly misused. For some it means no more than an education in the classics, which are often spoken of as the Humanities. In truth it is more than this. Aristotle gave the first definition of an intellectual and secular humanism, and since his day, and particularly at the time of the Italian Renaissance, there have been both secular and Christian concepts of humanism. For secular humanism the ideal is the cultivation of the mind, of intellectual excellence as an end in itself. Christian humanism weaves the Christian ethic into this concept.

The Christian world inherited from the ancient world an ideal of culture which had three aspects: a speculative aspect, the ideal of truth, a moral aspect, the ideal of virtue; and a literary aspect, the ideal of eloquence.

These three ideals are the essence of humanism properly considered. On the speculative side it strives for that lesser perfection of the reason which is ordered knowledge, scientia: and also for that higher perfection which is sapientia by which we place knowledge in the whole framework of life. On the moral side, it includes practical wisdom, that is, prudence.

Now while knowledge deals, as Aristotle says, with universals and things that are of necessity, prudence deals with the affairs of men—not with universals but with particulars. Thus it demands experience.

Now in the application of science to the practice of medicine we need prudence, for the doctor's action must have regard to the whole good of the individual patient. This regard is the essential act of the virtue of prudence and comes within the category of moral excellence. For the physician who is not a mere materialist, the whole good of man is more than his material welfare, and man himself is more than an animal and has a destiny beyond his sojourn in this world. It is in the light of this destiny that we should strive as physicians to serve him, and in so doing we transcend our role as scientist and historian.

In so far as we think of medicine as no more than the application of science for the restoration of, or the preservation of, his health as an economic unit merely, we have a debased conception of medicine, which will end with our becoming repairing and maintenance engineers to that bleakest of abstractions from the totality of the human person, economic man, and we shall be treated by society as being what we shall have become, a category of mechanics, 'rude mechanicals that work for bread' in Shakespeare's words.

I submit, then, that medicine embraces the natural sciences and historical

science, and that, properly conceived, it is lifted above these and gains its essential and distinguishing virtue amongst the professions as a humanist profession, taking the loftiest view of the human person as one having here no abiding city but a destiny which is his alone in the universe.

The profession of medicine flourishes most when doctors take a high view of their functions and responsibilities.

Thomas Linacre, who founded the Royal College of Physicians in the reign of Henry the Eighth, 400 years ago, and is still more famous as being the reintroducer of Greek learning into England, also founded a lectureship at Cambridge which is still annually given at St. John's College. It was my privilege to give it in 1950, and I ventured to remind my audience of the reasons Linacre gave for the foundation of these lectures. These were as follows: 'that they should rebound to the glory of God, the relief of the fallen and the increase of the 'realm'.'

In this bleak mechanical age in which we live, I am old-fashioned enough to believe that no nobler ideal of the vocation of the true physician could be proposed.

The intellectual vigor and moral elevation of our profession can be preserved only for so long as we cherish intellectual and moral ideals, and take a higher view of our functions than our technical skill and the safe provision of our material necessities and gratifications. Once we allow these to dominate our conscious aims, decadence will already have claimed us for its own, and we shall end by becoming clever technicians devoid of humanity and prudence.

It may perhaps seem odd that I should put these considerations before you, but I do so in the certainty that in the school of Osler and of Thayer, it will not seem out of place that I should do so, for where have these ideals been more nobly professed and performed than in this school? It is surely good for us from time to time, and especially on such an occasion of retrospect as this, that we should reconsider our ideals and renew our confession of faith in ourselves as worthy successors of those who have given us traditions, which, however the face of medicine changes, will remain imperishable.

SYNCOPE, VERTIGO AND DISTURBANCES OF VISION RESULTING FROM INTERMITTENT OBSTRUCTION OF THE VERTEBRAL ARTERIES DUE TO DEFECT IN THE ODONTOID PROCESS AND EXCESSIVE MOBILITY OF THE SECOND CERVICAL VERTEBRA

FRANK R. FORD

Received for publication June 2, 1952

The purpose of this paper is to present the case history of a young man who was subject to repeated episodes suggestive of disturbances in the hind brain, and to present evidence that these symptoms were due to a very unusual cause, i.e., *intermittent obstruction of the vertebral arteries.*

Case History (No. 529697) *A boy of 17 years developed attacks of syncope, followed by vertigo, unsteadiness, nystagmus and diplopia, which were sometimes induced by forcing the head backward, but often occurred for no apparent reason. Roentgenograms of the cervical spine revealed a defect in the odontoid process. The application of a cast to immobilize the head relieved the symptoms. Operation revealed excessive mobility of the second cervical vertebral. Fusion of the upper cervical spine was followed by complete relief of symptoms.*

The patient, G. T., Jr., was seen first in consultation with Dr. John T. Howard on February 8, 1950. He was then 17 years old. The patient was not a gifted witness and all the facts were not elicited immediately, but came to light during the next few months. For the sake of brevity, however, the whole history will be given at once. Since the summer of 1949, that is for a period of about six months, the patient had been subject to recurrent episodes during which he lost consciousness. These occurred at irregular intervals. He sometimes had several in one day and again might be free of symptoms for a week. The duration was usually only a few minutes but on several occasions he was unconscious for an hour. There were never any convulsive movements or rigidity. As a rule, the patient had some warning and was able to lie down, but sometimes the onset was so abrupt that he fell to the floor. The seizures never developed when he was lying still in bed, but often occurred when he got up from his bed or even from a chair. It is of interest that on three occasions he lost consciousness when his head was pushed back during a wrestling bout with a friend. In one such episode he was unconscious for an hour and subsequently had several less prolonged periods of unconsciousness. Another attack was apparently induced by lifting a heavy weight to his shoulder. However, many attacks seemed to develop without any apparent cause.

After regaining consciousness the patient was often confused and incoherent for a short time. On three occasions he displayed a horizontal nystagmus of large amplitude on lateral gaze. He was unsteady in station and gait and some-

what ataxic. When placed on his feet, his face would grow pale and he would complain of being dizzy. When permitted to lie down, he would regain his color and say he was comfortable once more. He complained of double vision in many of these episodes. Once his parents noticed deviation of one eye. He also complained of blurred vision at times. This was not relieved by closing one eye.

There were also many attacks of dizziness, without loss of consciousness. These seemed to be of the same nature as the episodes described above, but less severe. There might also be unsteadiness, blurring of vision, diplopia, pallor of the face and a feeling of faintness.

Twice, after wrestling and becoming unconscious the patient complained of prickling feelings in his hands and face, but never mentioned such sensations in his legs.

The patient had frequent and severe headaches, at certain times. These did not seem to be constantly associated with the other symptoms and there was some reason to think that they were provoked by nervous tension.

The past history cast no light on the cause of the patient's symptoms. There was no history of a serious injury. The patient had always enjoyed excellent health.

As one may easily imagine, no proper diagnosis could be made at that time. We considered the possibility of syncope, epilepsy, hypoglycemia, neoplasm, cyst or angioma in the posterior fossa and a psychogenic condition. Many examinations were made. Roentgenograms of the skull revealed no abnormalities. Dr. Otenasek performed two pneumoencephalograms with completely negative results. The second was made to secure clear visualization of the fourth ventricle and posterior fossa. The electroencephalogram and the electrocardiogram were considered normal. The carotid sinus reflexes were tested repeatedly, without result. No significant alterations in the blood pressure were discovered in connection with changes in posture. The glucose tolerance test revealed a normal curve. Many other examinations were made, but need not be enumerated since they were not helpful.

A series of anticonvulsive drugs was administered. Dilantin, phenobarbital, mebaral and mesantoin were employed without result. Ephedrine was also tried but no improvement resulted.

At this time, i.e., July, 1950, the patient was inducted into the service and sent to the Great Lakes Training Center. He became unconscious while on the train near Chicago and was removed to a hospital, where he was placed in the care of Dr. Paul Bucy. A few mild attacks were observed. A careful and complete examination was made with few positive results. An insulin tolerance test provoked an hypoglycemic reaction when the blood sugar fell to 30 mgs. Dr. Bucy did not regard this as significant. An electroencephalogram was

made by Dr. Frederic Gibbs, who described 14 and 16 per second spike seizure discharges maximal in the right temporo-occipital region. The background activity was normal. Dr. Gibbs interpreted this record to indicate a subcortical type of epilepsy. Bromides were prescribed.

The seizures continued. The patient could not return to school or hold a job. He was bewildered by his symptoms and lost confidence in himself. He

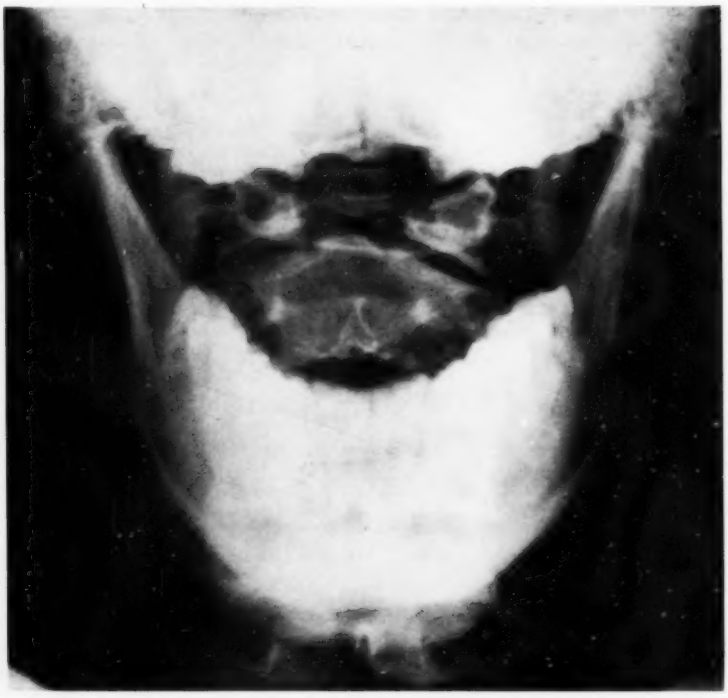

FIG. 1. Roentgenogram of the cervical spine showing absence of the major part of the odontoid process. The distal fragment casts a faint shadow which is not visible in this illustration.

thought, no doubt, correctly, that his friends considered him a peculiar fellow. A psychiatrist was consulted. He concluded that the boy was suffering from an emotional disturbance but was unwilling to say the symptoms were all psychogenic. Several interviews occurred, but the patient and his parents were sceptical of psychotherapy, though anxious to cooperate.

At this point, in September, 1950, the parents were much discouraged and in their dispair, took the patient to a chiropractor. We were not astonished to hear soon afterwards that a defect was found in the cervical spine. The parents,

however, took this report seriously and had studies made by several radiologists. It was found that the odontoid process was almost entirely absent as the accompanying illustration shows. Only a remnant of the base could be seen and a small fragment lying above which was completely detached from the base, or, at most, attached by fibrous connections. There was some difference of opinion among radiologists as to whether this condition represented a congenital defect, or was the result of an old fracture.

The patient was next taken to Dr. Earl Walker and entered the hospital for study on July 2, 1951. Carotid arteriograms were performed to exclude a vascular anomaly. An attempt to perform a vertebral arteriogram failed. More complete tests for metabolic disorders were made but nothing significant was brought to light.

In an effort to connect the symptoms with the abnormality of the cervical spine, the possibility was now considered that excessive mobility of the axis might cause compression or angulation of the vertebral arteries and thus produce the patient's symptoms. It was clear that direct compression of the cervical cord could not be responsible. Dr. Raymond Lenhard was requested to have a collar made to immobilize the patient's neck. The patient found this collar uncomfortable and could not be induced to wear it. Therefore, on January 22, 1952, a cast was applied which could not be removed. Three days later the boy experienced some discomfort in his neck and began to twist the cast and turn his head about as far as possible. A headache developed and some slight dizziness. After this he wore the cast patiently and was completely free from all symptoms until March 10th, when the cast was removed. Before the cast was applied he was having several attacks a day. After the cast was removed he soon experienced a return of the usual symptoms. The parents and the patient were quite satisfied that the cast had given relief.

It was decided that operative fusion of the upper cervical vertebrae was justified and indeed, required. On April 14, 1952, Dr. Raymond Lenhard operated. He found that the axis was quite loose and an excessive range of movement was easily demonstrated. No ligamentum flavum was seen at the level of the operation and the cord was covered by only a thin membrane. Segments of the vertebral arteries were seen and no vascular anomalies were observed. The axis was displaced so easily that Dr. Lenhard was unable to perform the fusion until it had been immobilized by an assistant. Four grafts were removed from the ilium and were employed to fix the axis to the first and third vertebrae. There were no post-operative complications.

Since the operation the patient has remained free of all symptoms.

DISCUSSION

To support the diagnosis indicated above, i.e. intermittent obstruction of the vertebral arteries, it is necessary to show that the symptoms may be ex-

plained on that basis and to offer evidence that such obstruction actually occurred.

The first problem does not seem difficult. If one remembers that the basilar artery is formed by the junction of the two vertebral arteries and that the posterior cerebral arteries arise from the basilar, it is evident that the medulla, pons, cerebellum and midbrain all derive their nutrition from blood which flows through the vertebral arteries. It seems quite plausible therefore to conclude that syncope, vertigo, nystagmus, unsteadiness, blurring of vision and diplopia may result from transient reduction of blood flow in one or both vertebral arteries.

At this point it is necessary to mention some anatomical relations of the vertebral arteries. In their second portion the vertebral arteries ascend through the transverse foramina in the transverse processes of the first six cervical vertebrae. As these arteries traverse the foramina in the axis they abandon their previous course which was almost vertical and pass upwards and outward to reach the foramina in the atlas. As they emerge from these foramina they pass horizontally to the outer side and back of the atlas and enter the suboccipital triangle. They then penetrate the posterior occipito-atlantoid ligament and enter the spinal canal. Thus, it is evident that the vertebral arteries pass through a series of superimposed bony rings which normally have a limited range of movement in relation to each other. It is obvious that excessive displacement of any one of these vertebrae may cause stretching, angulation or compression of the arteries. It has been shown by roentgenographic study and was also demonstrated at operation that excessive mobility of the axis was present in this case. The fact that immobilization of the neck by a plaster cast and later fixation of the loose vertebra by operative fusion abolished the symptoms would seem to offer strong evidence that excessive mobility of the axis was responsible for the patient's troubles.

It must be admitted that no objective proof of obstruction of the vertebral arteries is available. It is possible that such proof might have been secured if vertebral arteriograms had been performed when the head was placed in various positions. We did not have the courage to attempt this demonstration. I believe, however, that the facts given above offer convincing evidence that transient obstruction of the blood flow through the vertebral arteries did in fact occur.

A paper published by Pratt-Thomas and Berger in 1947 is of interest in this connection. These writers describe the findings in the post-mortem examination of three patients who developed cerebral symptoms during chiropractic manipulations of the neck and died soon afterwards. In one case, there was found thrombosis of the basilar, anterior and posterior inferior cerebellar arteries with corresponding softenings. In a second case, there was thrombosis

of the posterior inferior cerebellar, basilar and vertebral arteries. No fractures or dislocations were found. Since the symptoms are said to have developed during the manipulations, one would imagine that the arteries were damaged in some manner and the thromboses developed later. I have examined two patients who also had violent symptoms referable to the brain stem during such a manipulation of the neck. They both survived but displayed persisting signs of brain stem damage. These patients stated that it was sudden, violent rotation of the head which caused the trouble. In my opinion, it is impossible to explain these lesions except by the assumption that the vertebral arteries were damaged in some manner. I imagine that the arteries were stretched and lacerated with resulting thrombosis.

Dr. George Bennett tells me that he recalls two patients who, following fracture of the odontoid process, would grow weak and faint when they made certain movements of the head. Roentgenographic study revealed excessive mobility of the upper cervical spine and fusion gave complete relief.

No doubt the vertebral arteries are sometimes injured in fractures and dislocations of the cervical spine and this injury may be responsible for a fatal outcome in some instances.

SUMMARY

An unusual case history is given. It is that of a young man of 17 years who was subject to attacks of syncope which were followed by nystagmus, diplopia, blurring of vision, and unsteadiness. It was found that the odontoid process was missing and that excessive mobility of the second cervical vertebra was present. It was not decided whether this defect in the odontoid process was a result of injury or a defect of development. Immobilization of the neck by a plaster cast and later by operative fusion gave complete relief of the symptoms. Evidence is presented to show that displacement of the axis led to transient obstruction of the vertebral arteries and that interruption of the circulation of the brain stem was responsible for the symptoms.

It is suggested that this condition, i.e. obstruction of the vertebral arteries, may occur in cases of fracture or dislocation of the cervical spine.

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PASTEURELLA MULTOCIDA AND BRONCHIECTASIS

Report of Two Cases

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Human infection with *Pasteurella multocida* is uncommon. Schipper (1) summarized the literature from 1930 to 1947, during which time forty cases were reported. The organism was isolated from sputum or pleural exudate in fourteen patients. Only two of Schipper's cases occurred in the United States. Both cases followed animal bites, and *Pasteurella multocida* was isolated from abscesses. Since that time Needham (2) has isolated the organism from eleven patients at the Mayo Clinic, six of whom had bronchiectasis. Neter *et al.*, (3) described the isolation of the organism from a localized infection on the face. Zeller and Lepper (4) reported two cases of meningitis caused by a Pasteurella other than *Pasteurella tularensis* or *Pasteurella pestis*. The present report describes the isolation of *Pasteurella multocida* from two cases of bronchiectasis, one of which has subsequently been shown to be complicated by pulmonary tuberculosis.

Case #1. C. S., was a 59 year old white male veterinarian. His work for the past ten years consisted of inspecting swine and beef carcasses in a slaughter house. He had a chronic cough since the age of 23. There was no antecedent history of pneumonia or pertussis. He had never noted hemoptysis. About four weeks before admission to the Delaware Hospital, he had an influenza-like episode with an increased production of white sputum. Cultures of the sputum yielded a heavy growth of *Pasteurella multocida* which was sensitive to penicillin, aureomycin, terramycin, and chloromycetin. A bronchogram demonstrated bronchiectasis of the right lower lobe, especially the medial and posterior basal segments. He was treated with 6,400,000 units of aqueous penicillin over the course of three days.

A sputum culture following therapy was negative for *Pasteurella multicida*. Two weeks after treatment the sputum had returned to its previous characteristics in amount, color, and consistency.

Case #2. M. F., a 64 year old farmer, was admitted to the Delaware Hospital on October 19, 1950, complaining of fever, chills, chest pain, and hemoptysis. The complaints began three days before admission. He had a chronic cough for thirty years. There was neither a family history of tuberculosis nor a known contact with tuberculosis.

On admission his temperature was 103°F., and he had a tachycardia of 130 beats per minute. There were fine and course rales over the right chest posteriorly; bronchial breath sounds were present over the left apex; and clubbing of the fingers was noted. There was a moderate leucocytosis (12,000), with a shift to the left in polymorphonuclear leukocytes.

Three 24 hour sputum concentrates and three gastric aspirations were negative for tubercle bacilli. The first strength tuberculin skin test (P.P.D.) was positive, three plus.

Pulmonary tuberculosis was suspected because of several small cavities seen in the left apex on the chest X-ray. The right basilar segments had a mottled appearance, and bronchiectasis of the right basal segments was demonstrated by bronchography. *Pasteurella multocida* was cultured from secretions obtained at bronchoscopy, and was found to be sensitive to penicillin, aureomycin, terramycin, and chloromycetin.

The acute illness responded to parenteral procaine penicillin, (300,000 units daily) and the patient was afebrile within 72 hours of admission. After 10 days of penicillin therapy a sputum culture was negative for *Pasteurella multocida*. After three weeks of hospitalization, and at the time of discharge, his cough was productive of approximately one ounce of white sputum daily.

On March 26, 1951, he was again admitted with fever, general malaise, and increased productivity of sputum. He had a weight loss of ten pounds in five months. There were rhonchi throughout both lung fields and fine rales were present over the right base.

Pasteurella multocida was again isolated from the sputum culture. The serum agglutination titre was positive through a dilution of 1:160 for the homologous strain of *Pasteurella multocida*. A sputum culture obtained after seven days of treatment with penicillin was negative for *Pasteurella multocida*. *Mycobacterium tuberculosis* was also obtained from a sputum culture, and the patient was subsequently transferred to a sanitorium for therapy.

SUMMARY OF BACTERIOLOGY

The strains of *Pasteurella multocida* isolated from patients C. S. and M. F gave the same biochemical reactions as those described by Schipper, and corresponded to descriptions in Bergey's "Manual of Determinative Bacteriology" (5). Distinguishing characteristics included the fermentation of glucose, sucrose, xylose, and mannite with acid and no gas; production of indol, typical odor, sensitivity to penicillin and inhibition of growth on desoxycholate agar, due to the presence of the bile salt.

Cultural study demonstrated two growth phases in the strains isolated from patient M. F. on both hospital admissions. When first isolated, the organisms produced relatively large, raised colonies which showed a marked tendency to become confluent. These colonies flattened out, became viscous, and showed a raised ring at the periphery after 48–72 hours incubation. This is typical of colonies of an encapsulated organism in the mucoid or "M" phase. Capsules were demonstrated in india ink preparations from such colonies. These colonial characteristics were most marked on Difco G.C. chocolate agar, on which the pasteurella grew luxuriantly. The "M" form has been maintained on this medium, without variation, for one year. After several transfers on human blood agar plates, however, a second colony type appeared. These colonies were smaller, raised, discrete, smooth or "S" type colonies, easily distinguishable from those of the "M" form, and were composed of unencapsulated organisms.

Smears of the "M" type colonies showed Gram-negative coccobacilli with marked bi-polar staining, and resembled diplococci. Smears of the "S" variant

showed short, slender, Gram-negative bacilli with little or no bi-polar staining. The two forms also differed in virulence for mice; the "M" form regularly killed 50 per cent of mice injected intraperitoneally, while intraperitoneal inoculation of the "S" form produced an illness of several days, but all mice recovered.

The serologic reactions of the strain of *Pasteurella multocida* isolated from patient M.F. also varied with the growth phase. Rabbit antisera prepared by Dr. Schipper (1) against strains of *Pasteurella multocida* isolated from wild rats were available. The antisera weakly agglutinated the mucoid form of the M. F. strain to a titre of 1:80. The smooth form, however, was strongly agglutinated to a titre of 1:5120. Serum from patient M. F., obtained during the second hospital admission in March, 1951, 10 days after the recurrence of active symptoms and 5 months after the original admission, agglutinated both the "M" and "S" forms of the homologous strain of pasteurella to a titre of 1:160. The "S" antigen showed better agglutination than the "M" form. This serum failed to agglutinate the strain isolated from patient C. S.

The strain of *Pasteurella multocida* isolated from the sputum of patient C. S. produced typical "M" type colonies and has shown no variation in colony form to date. It regularly killed 100% of mice inoculated intraperitoneally. This strain was not agglutinated by the rabbit pasteurella antiserum. This failure to agglutinate may be due to a serologic difference between Schipper's strain of *Pasteurella multocida* from rats and the human strain isolated from patient C. S. Another possible explanation is that the rabbit antisera was probably prepared against stock strains of pasteurella in the "S" phase. This is suggested by the strong agglutination of the "S" form of strain M. F. and the weak agglutination of the unstable "M" form of strain M. F. The strain isolated from patient C. S. appears to be well stabilized in the "M" form and agglutination with antiserum containing antibodies against the "S" antigen would not be expected.

Serum obtained from patient C. S. fourteen days after the onset of the illness failed to agglutinate both the homologous strain of *Pasteurella multocida* and the "M" or "S" forms of the M. F. strain of pasteurella.

SUMMARY

1. *Pasteurella multocida* was isolated from the sputum of two patients with bronchiectasis.

2. The isolation, identification, and serologic reactions of the *Pasteurella multocida* are described.

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LESIONS IN AURICULAR APPENDAGES REMOVED AT OPERATIONS FOR MITRAL STENOSIS OF PRESUMED RHEUMATIC ORIGIN*

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In performing the operation for mitral commissurotomy, the left auricular appendage is amputated. A specimen, ordinarily 1.5 to 2.0 cm. in length, is obtained. Such material provides an unparalleled opportunity to study a portion of the heart from the living subject and to correlate morphological changes, if any, with the present and past clinical course.

This report is based on left auricular appendages removed at operation from 43 cases having what was clinically thought to be "pure" mitral stenosis, resulting from the rheumatic state. All of the operations were performed by Dr. Alfred Blalock. Naturally a history of a previous rheumatic episode was not obtained in every case. As the subjects were carefully selected, the resulting group is a specialized one. The age incidence ranged from 21 to 48 years with an average age of 34 years. There were 12 males and 31 females.

Before considering the results of the microscopic examination together with a clinical correlation of this material, we should like to describe and illustrate (Figures 1–14) characteristic examples of the lesions which have been encountered in order that what is to follow will be more intelligible. These changes will be taken up under the three regions: epicardium, myocardium and endocardium.

Epicardium: The alteration here consists of varying degrees of fibrous thickening with or without round cell (predominantly lymphocytic) infiltration in the underlying tissue. This lesion is entirely non-specific (Figure 1).

Myocardium: Three types of change have been delineated: hypertrophy of muscle fibers, perivascular scarring and distinctive rheumatic lesions. Varying degrees of hypertrophy of the fiber may be encountered. In addition to an increase in fiber width, a definite enlargement of the nucleus is a prominent part of the hypertrophy. These changes have been graded as to severity (Table I). Perivascular scarring may be prominent, in the absence of any cellular reaction, as is illustrated (Figure 2). Cellular infiltrations leading to lesions which are distinctive of rheumatic fever are shown in Figures 3 and 4.

* A portion of the data included herein was presented at a meeting of the Johns Hopkins Medical Society, Nov. 12, 1951 (1).

TABLE I

CASE NO.	AGE AND SEX	AGE OF ATTACK	CORR. SED. RATE	AURIC. FIBRIL.	PATHOLOGICAL LESIONS								
					Pericardium		Myocardium			Endocardium			
					F.T.[1]	R.C.I.[2]	Hyp.[3]	P.V.S.[4]	A.L.[5]	F.T.[1]	A.L.[5]	R.C.I.[2]	Thrombi
1	31 M	3, 14	23	+			+			2+	+	2+	+
2	37 F		27					+		2+	+		
3	34 F		18		+	3+	2+	+	4+	2+	3+		
4	32 M	13	0	+		+	+	+		2+	+	+	+
5	28 F	6, 20	10	+		+	+	+		2+	+	+	
6	37 F	12	11			+				2+			
7	35 F	4	9	+			+	+		3+			
8	30 F		1			+	+			2+			+
9	43 F	7, 9	19	+			+		3+	+	3+		+
10	46 F		12	+			+	+		+		+	
11	39 F		0			+		+		3+			
12	38 M	6	4			+			+	2+		+	+
13	28 F	*	0				+	+		+	+		
14	33 M		0				+			+	+		
15	42 M	4	34	+	3+		2+	+	2+	+	2+	3+	+
16	36 M		0			+	+	+		+	2+		
17	39 F	7	0			+		+	2+			+	
18	27 F	7, 16	5				+			+	+		
19	37 F		0				+			+			
20	40 F		4	+		+	+			3+	2+	+	+
21	25 M		9				+			3+	3+	+	
22	24 F	5	30		+	+	2+	+	4+	2+	4+		
23	40 F	12, 14	0	†			+	+		2+	+		
24	25 F	11, 13	1					+		2+	+	+	+
25	21 M		1				+	+	+	+	3+	+	
26	47 F	33	5	+			+				3+	+	
27	27 F	9	16				+				2+		
28	45 F	5, 30	0			+	3+	+		+		+	+
29	33 F	9, 29	12				+			+			
30	38 M	10, 18	12				2+			+	2+	+	
31	33 M	*	1				+	+	+		2+		
32	26 F	22, 24	5		+	+	+	+	+	+	+		
33	48 M	5	0	+	+	+	2+			+	2+	+	
34	34 F	*	12	+	+	+		+	+	+		+	+
35	35 F	5	0	+		+	+			2+	+	+	
36	24 M	12	0				+			2+			
37	22 F	16	9						+	+			
38	31 F		8			+	+	+		+	2+	+	
39	25 F		9				+			2+		+	+
40	33 F	12	2			+	+	+	4+	+	4+	+	
41	28 F	13	8	+							2+		
42	43 F		0	+		+	2+		+		2+		+
43	41 F		5	+									+

[1] F.T.: Fibrous Thickening.
[2] R.C.I.: Round Cell Infiltration.
[3] Hyp.: Hypertrophy.
[4] P.V.S.: Perivascular Scars.
[5] A.L.: Aschoff Lesions.
* Indicates history of severe sore throat.
† Developed auricular fibrillation after operation.

Such accumulations of cells may be perivascular in location or lie between muscle fibers and away from small vessels.

Endocardium: The endocardium in many instances is thickened. The most conspicuous alteration is the presence of Aschoff bodies of various ages in the subendocardial region as shown in Figures 5–14. These consist of stellate cells with characteristic basophilic cytoplasm arranged as small foci or as large aggregations of such cells intermixed with lymphocytes; some of the latter may be just beneath the intima of the endocardium. In some appendages organized as well as fresh thrombus material is found.

RESULTS

A summary of this series of cases is presented in Table I, where are listed data dealing with a history of a previous attack of rheumatic fever, the corrected sedimentation rate at the time of operation, and the presence or absence of auricular fibrillation. Together with this information the various lesions discussed and illustrated above are presented, graded as to severity. This grading was done quite independently of any knowledge of the clinical status of the patient.

TABLE II

Relationship of Presence and Severity of Lesions to Sedimentation Rate

	RHEUMATIC LESIONS	NO LESIONS
Elevated sed. rate	9	0
Normal sed. rate	23	11

A history of rheumatic fever was obtained in 25 subjects; in addition a history of severe sore throat was elicited in 3 others. Nineteen of those giving a positive story of rheumatic fever had characteristic rheumatic lesions. Nine of the 15 individuals from whom a history of a previous rheumatic episode had not been obtained showed lesions. The difference is hardly significant.

The sedimentation rates were corrected; normal values for males were taken as 0–6.5 and for females as 0–15 according to Wintrobe's criteria (2). The results are summarized in Table II. The more extensive lesions are found in those having an elevated sedimentation rate. No individuals having an elevated rate failed to show lesions.

Fifteen patients were fibrillating at the time of operation; all but 3 showed evidence of rheumatic involvement of either myocardium or endocardium. Of the 28 individuals who were not fibrillating 22 showed lesions, an incidence similar to that in the fibrillating group.

As will be seen in Table I, 13 specimens showed fresh and/or organizing

thrombi. Of this group of 13, 8 individuals were fibrillating at the time of operation.

DISCUSSION

As already noted the cases from which the anatomical material was derived were a specialized group. Certain criteria precluding operation have been formulated (3): bacterial endocarditis, obstructive disease of the aortic valve, intractable right heart failure, and mitral insufficiency of a significant degree. The presence of auricular fibrillation has not been deemed a contraindication for operation.

The presence in varying degree of microscopic evidence of the rheumatic state in this material has been of great interest to us. Of particular significance would appear to be the discovery of such morphological changes in patients who did not give a history of ever having had symptoms of a rheumatic episode, or if they did, had such a bout many, many years before. The relationship of characteristic lesions to the sedimentation rate is of further interest. No individuals had an elevated sedimentation rate who did not have changes; on the other hand lesions, though on an average of a lesser degree, were seen in individuals who did not have sedimentation rates above the upper limits of normal.

This brings us to a consideration of the meaning of the lesions which were encountered in so far as they indicate recent or current activity of the disease process. This is a difficult question to answer. In the past (4, 5) a great deal of attention has been directed at the relationship of lesions to former or current activity. Such studies have, of course, been based on autopsy material from which an attempt has been made to trace the life history of the Aschoff body and its changing morphology with time. Numerous sections taken from various areas of the ventricles and auricles have been available. In the present study such a broad survey is obviously impossible. Nor are we at all clear as to the relationship of lesions in the left auricular appendage to those found elsewhere in the heart, since in the surveys referred to above, little attention was given to the auricular appendages.

All that one can conclude is that in a certain number of individuals operated upon for mitral stenosis of presumed rheumatic origin, lesions which have been considered during the last half century as being characteristic of the rheumatic state may be encountered. It is fairly certain that such lesions are regressing ones.

In this study there does appear to be some correlation with the degree and extent of lesions and rise in sedimentation rate above normal values.

During the completion of this study reports have appeared dealing with an examination of auricular appendages amputated in the course of operations

for mitral commissurotomy. Ellis *et al.* (6) cite observations on 4 cases; 2 had lesions in the auricular appendage without changes in the remainder of the heart examined later at autopsy; while in 2 others having auricular lesions similar alterations were found elsewhere post mortem, shortly thereafter. Kuschner *et al.* (7) report Aschoff bodies in 4 of 11 specimens removed at operation from individuals, all of whom were considered to be clinically inactive. It is to be hoped that studies similar to the one herein reported and those in the literature will be carried out to gain further insight into the relationships of lesions and clinical manifestations of activity.

SUMMARY

A microscopic examination of 43 auricular appendages removed for the operation for mitral commissurotomy has been carried out. Lesions characteristic of rheumatic heart disease were found in 32 cases. The prevalence of such lesions has been correlated with certain clinical observations. The only positive correlation was with the sedimentation rate; individuals having elevated rates tended to have more extensive lesions than those whose rates were in the normal range.

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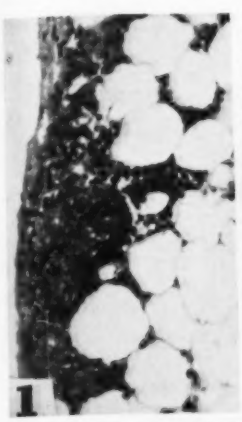
PLATE I

Fig. 1. Case 3. Focal accumulation of lymphocytes beneath epicardium, a non-specific reaction but one seen to some degree in almost half of the specimens examined.

Fig. 2. Case 22. Perivascular accentuation of hyaline connective tissue in the myocardium, a non-specific lesion observed in approximately one half of the specimens examined.

Figs. 3 and 4. Cases 9 and 15. Myocardial lesions consisting of accumulations of Aschoff cells.

Figs. 5 and 6. Cases 21 and 25. Small lesions in the endocardium and subendocardium consisting of Aschoff cells arranged in characteristic linear fashion.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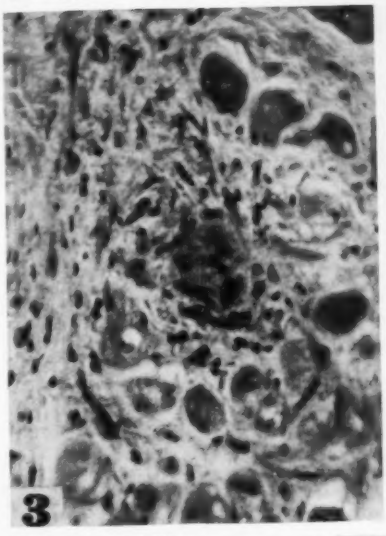
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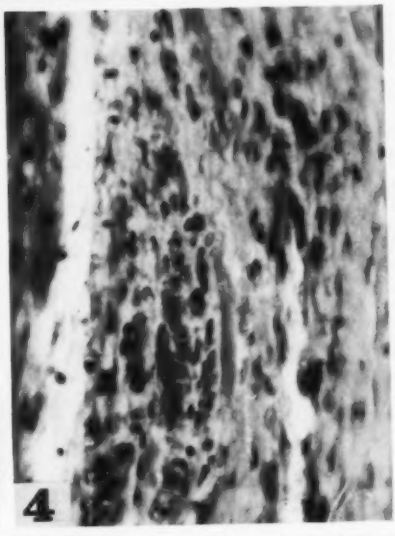
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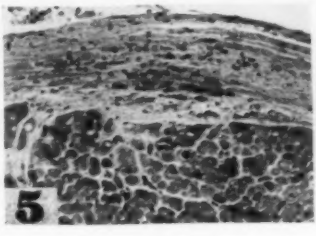
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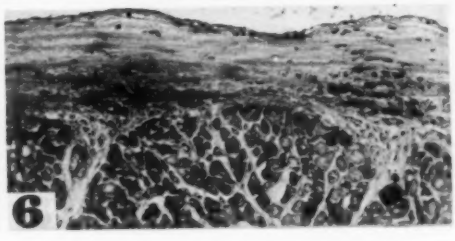
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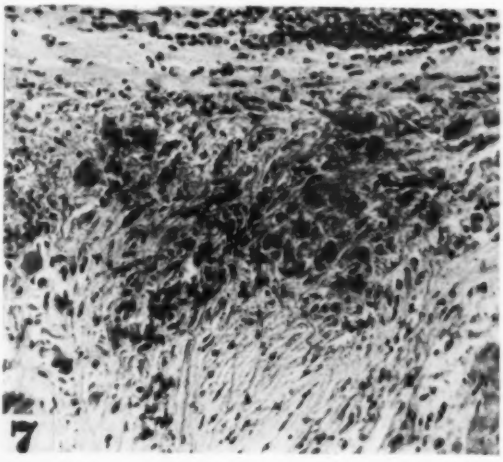
PLATE II

FIG. 7. Case 22. Aggregations of Aschoff cells in the endocardium and subendocardial region together with subintimal accumulations of lymphocytes.

FIG. 8. Case 40. Small focus of Aschoff cells with basophilic cytoplasm in subendocardial region.

FIG. 9. Case 22. Endocardial and subendocardium accumulations of Aschoff cells and lymphocytes.

FIG. 10. Case 25. Small focus of stellate Aschoff cells in subendocardial region.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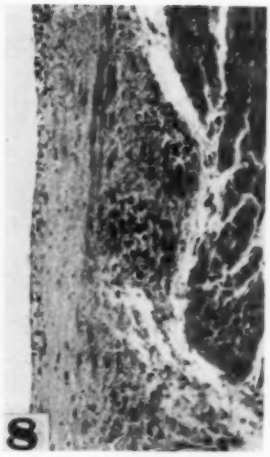
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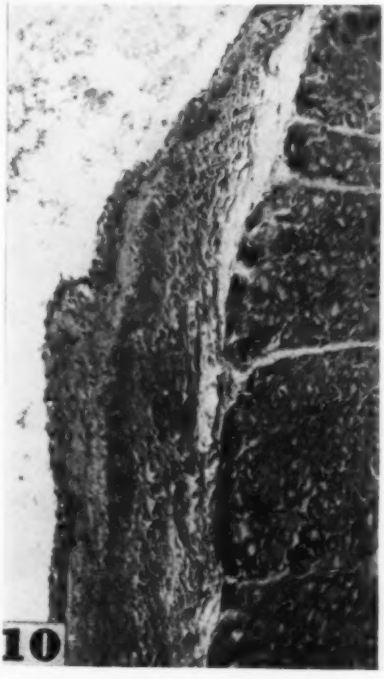
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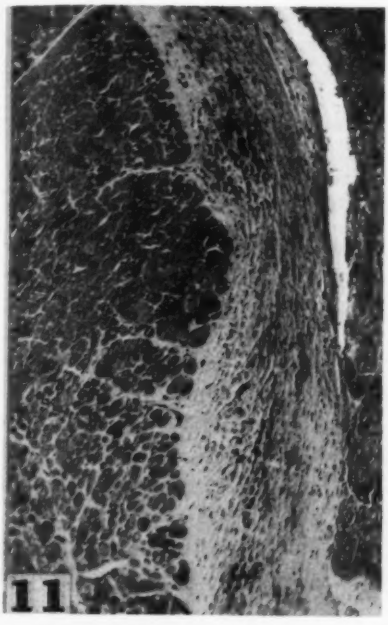
PLATE III

FIG. 11. Case 21. Foci of Aschoff cells in inner portion of endocardium. Edge of thrombus material may be seen at right.

FIG. 12. Case 31. Foci of Aschoff cells in thickened endocardium.

FIG. 13. Case 40. Aschoff nodule in thickened endocardium.

FIG. 14. Case 16. Small focus of Aschoff cells in subendocardial region.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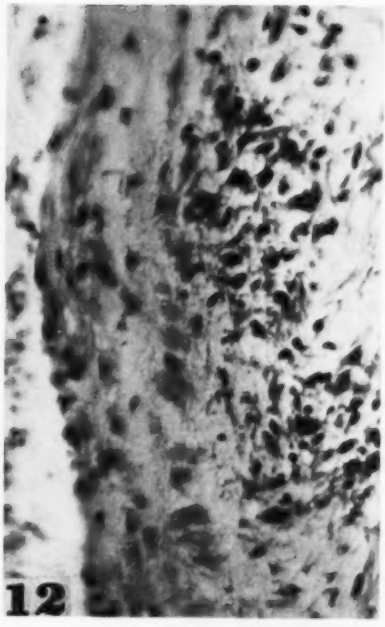
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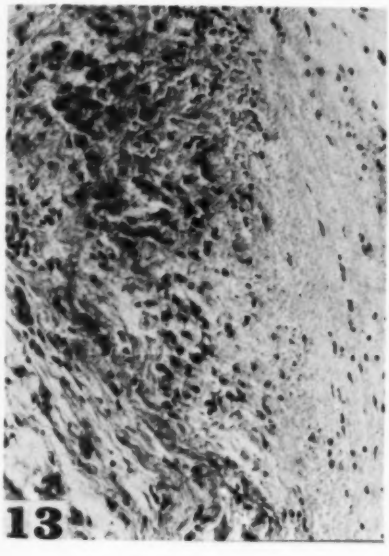
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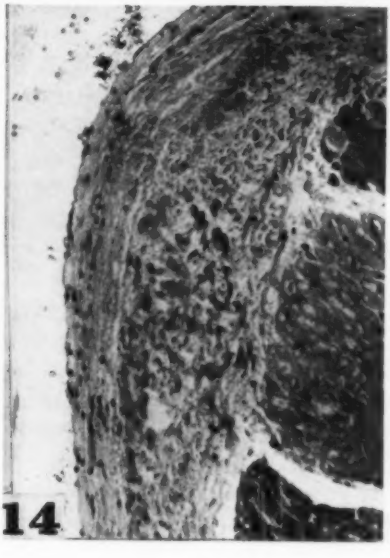
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OBSERVATIONS ON THE TRANSFORMATION OF PNEUMOCOCCUS IN VIVO

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The phenomenon of the transformation of pneumococcal capsular types was observed first in *in vivo* experiments performed by Griffith (1). Inoculating mice subcutaneously with a mixture of living, unencapsulated pneumococci derived from a strain of one capsular type and of heat-killed encapsulated organisms of a different capsular type, he was able to recover from mice succumbing to infection living encapsulated pneumococci of the same capsular type as the heat-killed encapsulated organisms apparently inducing the change. The validity of this experiment rested upon the demonstrable absence of viable cells from the vaccine of encapsulated pneumococci. With the recognition of the type-specific M proteins of pneumococcus (2) and of the fact that they vary independently of type-specific capsular polysaccharides (3), a method for the study of pneumococcal transformation reactions *in vivo* based upon antigenic recombination has become available. The demonstration of new combinations of M protein and capsular carbohydrate in pneumococci recovered from animals inoculated experimentally with transforming mixtures establishes with certainty the fact that transformation has occurred and excludes the possibility that viable encapsulated organisms persisting in the transforming vaccine led to the illness or death of the experimental animal.

The possible occurrence of pneumococcal transformation reactions under natural circumstances *in vivo* is of interest for several reasons. Analysis of the antigenic structure of pneumococci recovered from humans ill with lobar pneumonia reveals that strains of the same capsular type may be associated with different M proteins and that strains with the same M protein may be of different capsular types. These findings suggest that antigenic recombination may take place in nature. The more recent observations of Ephrussi-Taylor (4) on the genetic interaction of phenotypically similar, yet genotypically distinct, capsular variants of pneumococcus type III have epidemiologic implications which also make desirable further knowledge regarding pneumococcal transformation reactions *in vivo*. In these experiments, the reaction between the genetically active material of one strain of pneumococcus producing very small amounts of type III capsular polysaccharide with the cells of another phenotypically similar but genetically different strain led to the emergence of a fully

This work was supported by a grant-in-aid from the National Institutes of Health, Public Health Service, Federal Security Agency.

encapsulated strain of pneumococcus type III. This finding suggests that interaction between strains of low virulence may result in the appearance of a strain of heightened virulence, for it has been shown that virulence in pneumococcus is related directly to the quantity of capsular polysaccharide produced by the cell (5, 6, 7). Thus a mechanism has been demonstrated which may result in alteration of host-parasite relationships if transformation reactions do occur in nature. That very large numbers of bacteria are not necessary for the completion of the transformation reaction has been demonstrated recently by Hotchkiss (8) who has effected transformation with penicillin lysates of 10^5 pneumococcal cells.

The observations noted indicate the desirability of determining whether or not pneumococcal transformation reactions will occur in other mammalian species than the mouse and of investigating the bodily sites in which the reaction will take place.

MATERIALS AND METHODS

1. *Transformation Reactions in Vivo.*—The technique employed was that described originally by Griffith (1) as modified by MacLeod and Krauss (5). The quantity of the transforming mixture injected varied with the species of animal and the site of inoculation. Routine tests for the sterility of the transforming vaccines revealed all to be free of viable organisms.

2. *Species of Animal.*—

Mouse: white mice of the CFW strain.
Rat: white rats of the CF strain.
Guinea pig: stock laboratory animals of mixed pedigree.
Rabbit: stock laboratory animals of mixed pedigree.
Cat: domestic cats of mixed pedigree.
Monkey: *Macacus rhesus.*

3. *Strains of Pneumococcus.*—R36NC: an unencapsulated strain of pneumococcus derived originally from the fully encapsulated type II strain D39S. This strain produces the somatic M protein type 2′ and has strong alpha-hemolytic properties when grown on neopeptone-rabbit blood agar and on trypticase soy-human blood agar.

I-SVI: a fully encapsulated strain of pneumococcus type I[1] carried for many years in the laboratory. It produces the somatic M protein type 1 and gives rise to weakly alpha-hemolytic reactions on neopeptone-rabbit blood agar and on trypticase soy-human blood agar.

III-A66: a fully encapsulated strain of pneumococcus type III carried for many years in the laboratory. It produces somatic M protein type 3 and has weak hemolytic properties.

XIX: a fully encapsulated strain of pneumococcus type XIX, isolated from a patient with lobar pneumonia at the Johns Hopkins Hospital in 1951. The M protein of this strain has not been studied.

4. *Strains of Virus.*—Pneumonia Virus of Mice: PVM strain 15 isolated at the Rocke-

[1] The capsular typing sera used in this study were generously supplied by Lederle Laboratories Division, American Cyanamid Company through the courtesy of Dr. H. D. Piersma.

feller Institute for Medical Research. Mice were inoculated intranasally during light ether anaesthesia with 0.05 cc. of appropriate dilutions of suspensions of infected mouse lung.

Influenza A: strain PR8. Mice were inoculated intranasally during light ether anaesthesia with 0.03 cc. of appropriate dilutions of infected allantoic fluid.

The pneumococcal transforming mixture was administered to mice five days after infection with either virus.

5. *Preparation of Anti-M Sera, M extracts, and Techniques of Precipitin and Agglutination Tests.*—The methods used were those employed by Austrian and MacLeod (2).

EXPERIMENTAL

Pneumococcal Transformation in the Mouse.—White mice of the CFW strain were inoculated subcutaneously with 1.0 cc. of a mixture of 1 part living culture of pneumococcus R36NC and of 4 parts heat-killed transforming vaccine of pneumococcus I-SVI or III-A66. Of ten mice inoculated with the vaccine of pneumococcus I-SVI, eight succumbed to type I pneumococcal sepsis and of ten mice injected with a mixture containing the transforming vaccine derived from pneumococcus III-A66, two died of infection with pneumococcus type III. Of the type I strains recovered, seven possessed the M protein type 2′ of strain R36NC as did one of the two type III strains, demonstrating thereby antigenic recombination. The remaining type I and type III strains were found, on antigenic analysis, to possess the M protein types 1 and 3 respectively. When the hemolytic properties of the two latter strains were contrasted on the same blood agar plates with the hemolytic properties of pneumococcus R36NC and of the strains from which the transforming vaccines had been made, it was observed that the strains recovered from the mice possessed the strongly hemolytic properties of pneumococcus R36NC and differed sharply in this respect from the weakly hemolytic strains, I-SVI and III-A66. These findings, in the absence of demonstrable viable organisms in the transforming vaccines, leave little doubt that in these strains, double transformations had taken place with the acquisition both of type-specific capsular polysaccharide and of type-specific somatic M protein. The results are recorded in Table I.

A single attempt to induce capsular type transformation by injecting subcutaneously a mixture of live pneumococcus R36NC and of a partially purified solution of pneumococcal transforming principle prepared from strain III-A66 according to the method of MacLeod and Krauss (5) was unsuccessful. No encapsulated pneumococci were recovered from mice which received one hundred thousand times the amount of soluble transforming principle required to induce transformation *in vitro*.

Because the natural habitat of the pneumococcus is the respiratory tract, attempts were made to effect transformation therein. Normal mice and mice infected with the pneumonia virus of mice (PVM strain 15) or with the PR8 strain of virus influenza A were inoculated intranasally five days after initiation of the viral infection with 0.03 cc. of a transforming mixture containing

live cells of pneumococcus R36NC and a heat-killed vaccine of pneumococcus types I or III. Inasmuch as this small quantity of the transforming mixture failed to result in capsular type transformation when injected subcutaneously, it is not surprising that negative results were observed following intranasal instillation of this amount into mice with normal or diseased lungs. Control subcutaneous inoculations with larger quantities of the same mixtures did result in capsular type transformation in mice but the use of such volumes intranasally was precluded by their asphyxial effect. Nasal cultures of animals

TABLE I

Transformation In Vivo *of Pneumococcus R36NC**

MAMMALIAN SPECIES	ANTIGENS OF INDUCING STRAIN			PROPERTIES OF TRANSFORMED STRAIN		
	Strain	M protein	SSS	Hemolysis	M protein	SSS
Mouse	I-SVI	1	I	R36NC R36NC	2′ 1	I I
	III-A66	3	III	R36NC R36NC	2′ 3	III III
Rat	I-SVI	1	I	R36NC R36NC	2′ 1	I I
Guinea pig	XIX	—	XIX	R36NC	2′	XIX
Rabbit	I-SVI	1	I	R36NC R36NC	2′ 1	I I
Cat	I-SVI	1	I	R36NC	2′	I
Monkey	I-SVI	1	I	R36NC R36NC	2′ 1	I I

* This strain produces M protein type 2′ and has strong α-hemolytic properties. Strains I-SVI and III-A66 are very weakly hemolytic.

surviving intranasal inoculation of 0.03 cc. of the transforming mixture yielded small numbers of pneumococcus R36NC one, two and four weeks after inoculation. These organisms were shown to possess the type-specific protein M2′ of strain R36NC and to be competent in *in vitro* transformation reactions. The results indicate that unencapsulated pneumococci capable of acquiring a capsule through transformation may persist in the murine respiratory tract as long as four weeks.

Pneumococcal Transformation in the Rat.—Five albino rats of the CF strain were inoculated subcutaneously with 2.0 cc. of a transforming mixture of live pneumococcus R36NC and a heat-killed vaccine of pneumococcus I-SVI. Four days later, one animal succumbed to a generalized infection with bilateral

pneumonia, empyema and peritonitis due to pneumococcus type I. Determination of the somatic M protein of this strain revealed it to be type 2′, demonstrating antigenic recombination. Another strain of pneumococcus type I was recovered from the site of inoculation of the transforming mixture into a second rat sacrificed four days after injection. This strain was found to possess type 1 M protein together with the strongly hemolytic properties of pneumococcus R36NC which are not manifested by pneumococcus I-SVI. Inasmuch as no viable organisms were demonstrated in the transforming vaccine, it appears that transformation of pneumococcal M protein may take place in the rat as well as in the mouse. The remaining three rats were sacrificed two weeks after inoculation at which time they appeared well. No pneumococci were recovered from these animals, cultures from the site of inoculation proving sterile.

Pneumococcal Transformation in the Guinea Pig.—Four guinea pigs were inoculated subcutaneously with 3.0 cc. of a mixture of live pneumococcus R36NC and heat-killed transforming vaccine of pneumococcus type XIX. Pneumococcus type XIX was used because of the known susceptibility of guinea pigs to infection with this organism (9). The M protein of the strain employed was not identified but it gave no reaction with M2′ antisera. All four animals developed fever following inoculation. Culture of the site of inoculation of one animal sacrificed on the eighth day of the experiment yielded only pneumococcus R36NC. A second animal, sacrificed on the eighteenth day, had at that time a large abscess in its abdominal wall and areas of pulmonary consolidation from both of which sites type XIX pneumococci were recovered. On the twenty-second day of the experiment, a third guinea pig appeared moribund and was sacrificed. Type XIX pneumococci were grown from a small abscess in the abdominal wall. Antigenic analysis of the strains of type XIX pneumococcus recovered from the two guinea pigs showed both to possess type 2′ M protein in combination with type XIX capsular polysaccharide. No bacteria were isolated from the fourth guinea pig which died on the nineteenth day of the experiment.

Pneumococcal Transformation in the Rabbit.—Subcutaneous inoculation of four rabbits with 4.0 cc. of a mixture of live pneumococcus R36NC and a transforming vaccine of pneumococcus I-SVI resulted in the death of all four animals from type I pneumococcal septicemia within five days. The M protein extracts of heart blood cultures obtained from these animals reacted both with anti-M2′ and anti-M1 sera, a finding suggesting that the cultures were not homogeneous. When extracts were made from single clones isolated from the original heart blood cultures, they reacted either with anti-M2′ or anti-M1 serum but not with both. From three of the four rabbits, clones of type I pneumococci demonstrating antigenic recombination by virtue of their possession of type 2′ M protein were obtained. From the fourth rabbit, the only

clones examined possessed type 1 M protein. All the clones examined had the hemolytic properties of pneumococcus R36NC, differing markedly in this respect from pneumococcus I-SVI. It is of interest that from one rabbit, separate clones of type I pneumococcus possessing either type 1 or type 2′ M protein were isolated. This observation demonstrates that at least two cells underwent transformation in the same animal and that both capsular polysaccharide and somatic M protein may be acquired through transformation reactions in the rabbit.

Attempts were made to induce pneumococcal capsular type transformation in the respiratory tract of the rabbit by inoculating animals intratracheally with 4.0 cc. of the same transforming mixture used for subcutaneous inoculation. In none of five animals so injected was transformation demonstrated.

Pneumococcal Transformation in the Cat.—Subcutaneous inoculation of each of four adult domestic cats with 5.0 cc. of a mixture of live pneumococcus R36NC and transforming vaccine of pneumococcus I-SVI failed to result in the demonstration of pneumococcal transformation. Unencapsulated pneumococci were recovered from one animal from the site of injection three days after inoculation but not from the other three.

Inoculation subcutaneously of two kittens weighing approximately 500 grams each with 5.0 cc. of the same transforming mixture used to inject the adult cats resulted in the death of one animal and in an acute illness with convulsions in the other which was sacrificed twenty-four hours after infection. Intermediate capsular variants of pneumococcus type I were recovered from the local lesions and heart blood of both animals and from the spinal fluid of the animal with convulsions. These strains gave a small but definite quellung reaction with type I capsular antiserum by which they were agglutinated also. Both strains grew diffusely in anti-R serum. M protein extracts of both strains showed each to possess type 2′ M protein, demonstrating thereby antigenic recombination.

Pneumococcal Transformation in the Rhesus Monkey.—One male and one female rhesus monkey (*M. rhesus*) weighing approximately three kilograms each were inoculated subcutaneously with 3.0 cc. and 5.0 cc. respectively of a transforming mixture of live pneumococcus R36NC and heat-killed vaccine of pneumococcus I-SVI. Three weeks previously, the male animal had been inoculated intrabronchially[2] with 3.0 cc. of the same mixture following which procedure type I pneumococci had not been recovered by transthoracic puncture of the injected lung. Two days after subcutaneous inoculation, both animals were febrile and heart blood cultures revealed both monkeys to have type I pneumococcal septicemia from which they recovered spontaneously. In addition, aspiration of abscesses at the site of subcutaneous inoculation

[2] Appreciation is expressed to Dr. Donald F. Proctor for performing this procedure.

yielded type I pneumococci. Clones of type I pneumococci from the heart blood culture of each animal were examined and each was found to possess type 2′ M protein. Clones from the subcutaneous abscess of each animal, however, were found to be composed of cells containing type 1 M protein, yet manifesting the strongly hemolytic properties of pneumococcus R36NC. The results demonstrate that transformation of pneumococcal capsular type and M protein may take place in a primate and that more than one bacterial cell may be transformed in the same animal.

DISCUSSION

The experimental data reveal that the phenomenon of pneumococcal transformation is one that may be demonstrated in a variety of mammalian species including several rodents, a carnivore and a primate. The conditions used to induce pneumococcal transformation *in vivo*, however, are highly artificial and unlikely to be reproduced under natural circumstances. Inability to demonstrate transformation in the respiratory tract, the natural habitat of pneumococcus, may not indicate anything other than the fact that the experimental procedures employed were inappropriate; and a number of factors may have contributed to the failure of the experiments. Study of pneumococcal transformation *in vitro* reveals that a serum factor (10), present in bovine serum albumin (11), is essential to the completion of the reaction. It has been shown also, however, that mammalian sera manifest desoxyribonuclease activity which inhibits transformation by inactivation of the transforming principle (12). At present nothing is known regarding how the balance of these two antagonistic factors may influence transformation *in vivo*. Use of a heat-killed pneumococcal vaccine as a source of transforming principle is probably inefficient, for the destruction of the cells is slowed markedly by the inactivation of their autolytic enzymes and the amount of desoxyribonucleic acid released is doubtless small. The number of cells in the volume of transforming vaccine required for these experiments was more than one hundred thousand times the number necessary to yield an active lysate in the *in vitro* experiments of Hotchkiss (8). The bacterial vaccine, however, appears to provide local environmental conditions which are not duplicated by the use *in vivo* of soluble transforming principle in large excess, for transformation was not observed when the latter was employed. Another factor which may operate to influence the outcome of transformation reactions in the respiratory tract is the susceptibility of the transforming principle to reversible oxidative inactivation (13). This fact may make the lungs potentially a less suitable site than the paranasal sinuses for transformation reactions. Finally, the role of leukocytes in phagocytizing living unencapsulated cells in the transforming mixture requires consideration. In so vascular a structure as the lung, the accessibility of the unencapsulated

pneumococci to phagocytes which can engulf these invading bacteria readily in the absence of added antibody may interfere with transformation.

It appears, therefore, that though a considerable body of evidence supports indirectly the idea that pneumococcal transformation reactions may take place in nature and though the present studies reveal that the reaction may occur under artificial circumstances in a variety of mammalian species, the natural conditions under which this reaction may occur still await definition.

SUMMARY

The transformation of pneumococcal capsular polysaccharide and type-specific somatic M protein in a variety of mammalian species is described and the relation of these observations to the possible natural occurrence of pneumococcal transformation reactions is discussed.

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A PREVIOUSLY UNDESCRIBED CONGENITAL MALFORMATION OF THE HEART: ALMOST TOTAL ABSENCE OF THE MYOCARDIUM OF THE RIGHT VENTRICLE

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We have recently had the opportunity to study a unique case of congenital malformation of the heart in an eight month old infant. A careful search of the literature reveals that the lesion found is the first such developmental anomaly of the human heart to be described. It illustrates and confirms the observations of Davis (1) concerning the separate embryologic origin of the endocardium and valves and the myoepicardium of the human heart. In this heart, there is almost total absence of the myocardium from the right ventricular wall without any defects of the valves, a contrast to the usual finding in congenital heart disease of atresia of the associated valves whenever gross myocardial defects occur. Because of its unusual nature, this case is presented in detail.

A. F., (H. L. H. History No. A-57350) a white female infant of 7 months, was admitted to The Harriet Lane Home with the chief complaint that she had "turned blue" during her last feeding. Family history revealed that the patient was an only child of a healthy young couple; otherwise, it was essentially non-contributory. The child was the product of an uneventful pregnancy and a normal spontaneous delivery at the South Baltimore General Hospital, and weighed 6 pounds, 10 ounces at birth. For approximately the first two months of life vomiting followed almost every feeding, but no cyanosis was noted during the neonatal period; although the child was always somewhat of a feeding problem, she gained slowly. At four or five months the parents noticed rapid, gasping respirations, with an occasional dry cough. At times they also observed swelling of her feet and slight blueness about her lips when crying, but they had never observed generalized cyanosis until the day of hospitalization. On the afternoon of the day of admission, while being fed, the baby suddenly became intensely cyanotic, and was rushed to the Harriet Lane Home.

Physical Examination: Weight 7 kilos, height 63 cm., head 40 cm. in circumference, chest 42 cm., abdomen 49 cm., temperature 99.4°F., pulse rate 152, respiration 48. The blood pressure was not obtainable in either arm on admission, but was found later to be 130/100. The patient was well-developed and fairly well-nourished. She appeared puffy, cyanotic and moribund, and was in severe respiratory distress and peripheral collapse. There was a petechial rash of the extremities, chest and back. Pitting edema of the hands, feet, and pretibial area was present. The anterior fontanel admitted three fingers and bulged slightly. Examination of the eyes, ears, nose and throat was negative. The neck was supple. There was no generalized or local glandular enlargement. The chest was symmetrical. Percussion revealed marked widening of the area of mediastinal and cardiac dullness with hyperresonance of the lung fields posteriorly. Transient dry rales were present bilaterally. The heart sounds were distant and feeble, the rate was 152, and there was a gallop rhythm. No murmurs were heard. The abdomen was markedly distended and the liver was palpable three to four fingerbreadths below the costal margin. Large, firm masses

felt in both flanks were thought to be kidneys. The remaining physical examination was normal.

Laboratory Studies: Serological test for syphilis and the tuberculin skin test (0.1 mgm. O.T.) were negative. Blood count revealed 6.0 million red blood cells, hemoglobin 16.5 gms. (ranging during hospital stay from 12 to 17 gms.), and a white blood cell count of 8,080

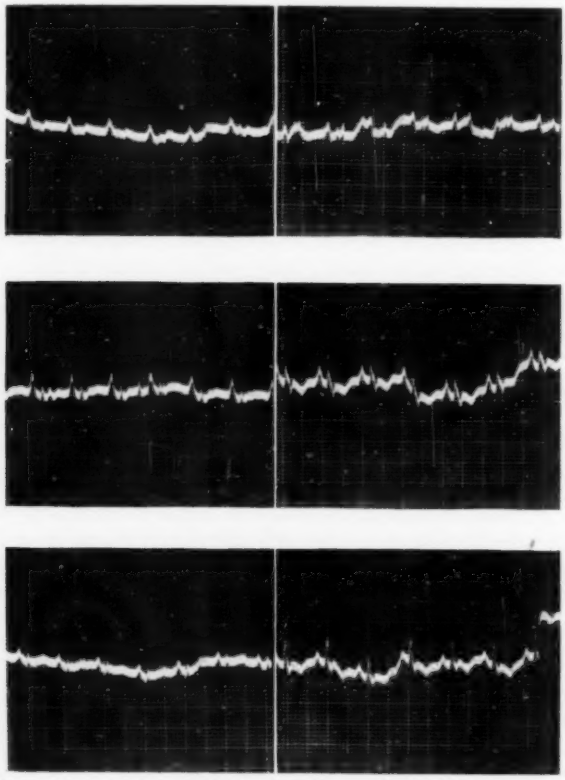

FIG. 1. EKG pattern is characteristic of and essentially similar to all tracings taken during the hospital stay of A. F. Standard leads I, II, III on the left, V leads 1, 3 and 5 on the right.

with a normal differential (ranging during the hospital stay from 8,000 to 12,000). The bleeding and clotting times were normal. The urine was clear and yellow in color, specific gravity ranged from 1.012–1.024, albumin from 1 plus to 3 plus; on occasions the urinary sediment showed a rare red blood cell with a few granular casts. Blood culture on admission grew *B. coli*, and urine culture on the 10th hospital day grew *B. aerogenes* and *Ps. pyocyaneus*. Culture of the spinal fluid on admission was negative, and fluid obtained from repeated pericardial and chest taps showed no growth. Initial blood chemistries revealed a non-protein nitrogen of 30 mg. %, total serum protein of 4.68 gms. % with a 2.9 A/G ratio. The non-protein nitrogen determination was normal until the terminal stage, when

it rose to 51 mgm. %; the blood calcium, phosphorus, phosphatase and cholesterol values were normal. The results of tolerance tests for glucose and adrenalin suggested the possibility of a disorder of glycogen metabolism; however, an I.V. glucose tolerance test did not substantiate the oral test. The cephalin flocculation test was negative, and the thymol turbidity test 7 units. Several electrocardiogram tracings revealed high peaked P waves, isoelectric QRS complexes, and the standard chest leads on only one occasion suggested left ventricular hypertrophy (Figure 1). The circulation time on the 11th hospital day was 10 seconds. Arterial oxygen saturation was 81.4% on the 31st hospital day. X-ray of the chest on numerous occasions revealed that the heart was grossly enlarged in all diameters (Figure 2)

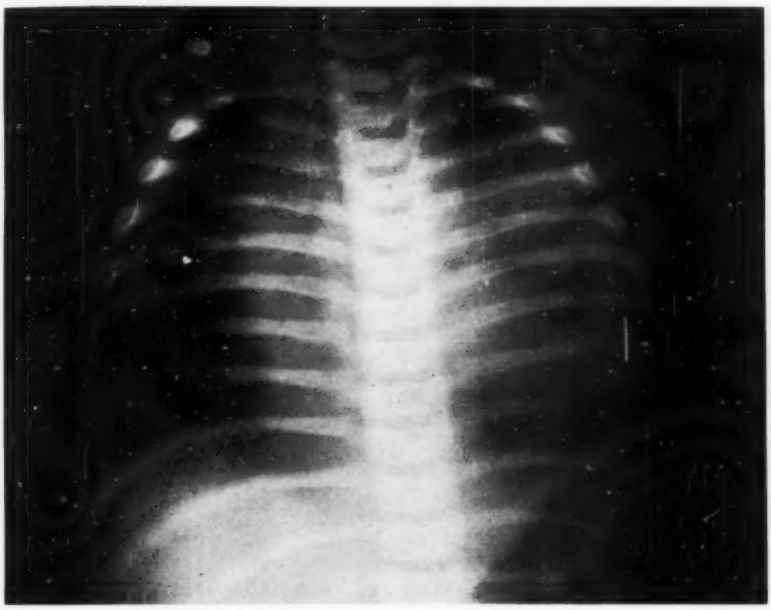

FIG. 2. Chest X-ray of A. F. Slightly lordotic angle on exposure.

and its density was globular in shape. Intravenous pyelogram studies done on two occasions revealed no abnormalities.

Hospital Course: On admission the patient was placed on oxygen, digitalized, and given penicillin and sulfadiazine; streptomycin was added following a blood culture positive for *B. coli*. Sulfadiazine and streptomycin were discontinued subsequently, but penicillin was continued throughout the hospital stay. The patient improved temporarily with oxygen, digitalis, mercupurin, salt-poor albumin, and ammonium chloride. For the most part her hospital course was febrile, the temperature ranging between 99°–102°F., with occasional spikes above 104°. During the last few days cardiac failure was not controlled, the temperature rose, and cyanosis and edema increased. The patient's respirations ceased on the 36th hospital day. The clinical impression was congenital heart disease or Fiedler's myocarditis.

Autopsy Report

(J. H. H. Autopsy No. 20838.) The body was that of a white female infant, 8 months old, measuring 65 cm. in length, weighing 7 kilos and only fairly well-nourished. The skin was pale. There was a cyanotic tinge to the lips, and moderate edema of the extremities.

The fat panniculus of the abdominal wall was edematous, and the abdominal cavity contained clear fluid. The liver was greatly enlarged, but grossly the other organs appeared

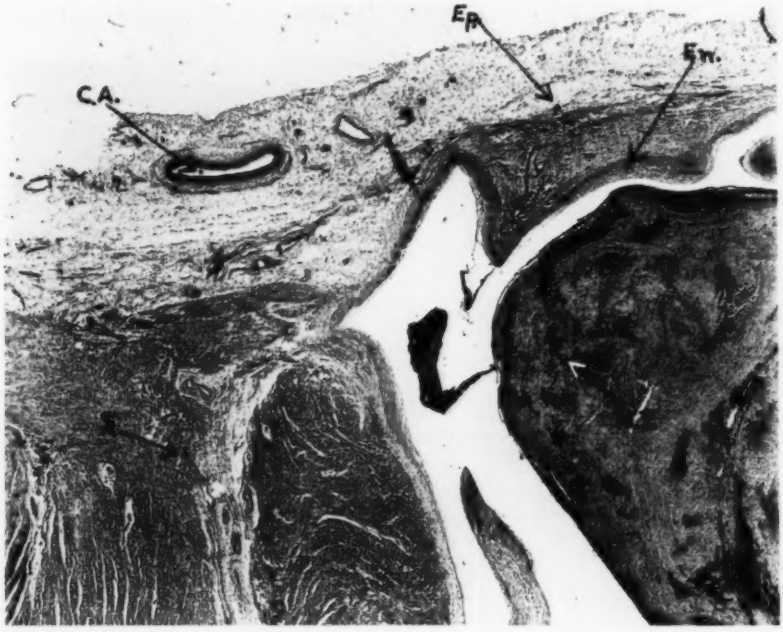

FIG. 3. Microscopic section of the heart taken from the anterior wall, including a portion of the septum and the right ventricle, demonstrates the primary defect in the wall of the right ventricle. Myocardium ceases at the junction of the septum with the right ventricular wall. The muscle of the septum appears entirely normal. In the wall of the right ventricle there is only endocardium and epicardium. Note the normal coronary artery (C.A.), septum (S), mural thrombus (M.T.), epicardium (Ep.) and endocardium (En.). ×15.

normal. Both pleural cavities contained a moderate amount of clear fluid, and the pleural surfaces appeared smooth and shiny. The pericardial sac contained a moderate amount of fluid, and together with its contents almost filled the left hemithorax. The pericardial surfaces were smooth and glistening.

Externally the heart appeared greatly enlarged but it was not weighed separately because it was preserved attached to the lungs. The epicardium over the auricles and left ventricle appeared normal, with a smooth, glistening surface and scattered deposits of soft yellow fat. However, over the surface of the right ventricle, especially a portion 1½

cm. below the auriculoventricular sulcus and extending to the apex, the epicardium, although smooth, appeared thickened and fibrous, with the fat deposits grey to dull white rather than yellow. The right auricle was greatly dilated and its wall hypertrophied with both myocardial and endocardial thickening. The endocardium, lacking its usual translucence, appeared dense and grey. The foramen ovale was completely closed and would not admit a fine probe; the fossa ovalis appeared normal. The tricuspid valve ring, measuring 4 cm. in circumference, was dilated, but the valve leaflets were delicate and translucent. The right ventricle was grossly abnormal. Almost the entire dilated chamber was occupied by a large laminated mural thrombus which adhered firmly to the endocardium

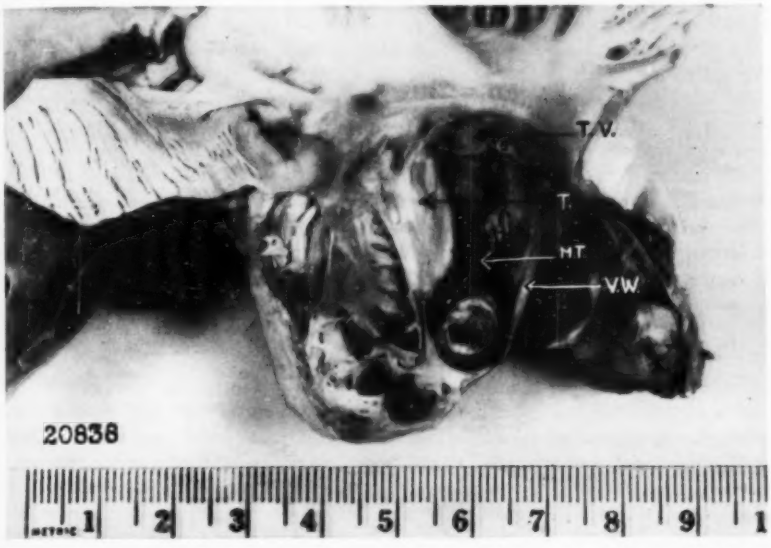

FIG 4. Photograph of the heart demonstrates the lesion of the right ventricular wall (V.W.) which is paper thin. On its endocardial surface is attached a huge mural thrombus (M.T.). Note the thickened endocardium over the broad, flat trabeculum (T.). The leaflets of the tricuspid valve (T.V.) are delicate. The wall of the right auricle is thickened and the chamber greatly dilated.

along the anterior wall of the ventricle. Examination of the cut edge of the ventricle wall revealed it to be paper-thin with no myocardium visible except at the base of the chamber adjacent to the tricuspid ring, at the pulmonary conus, in the septum and a small portion of the posterior aspect of the wall. The trabeculae carnae were invested with the thrombus and some of them appeared to be fused, forming a thick flat band on the septal wall. The papillary muscles appeared intact and their attached chordae tendinae were normal. The pulmonary valve was normal in form and the three valve cusps showed no thickening (Plates 1 and 2; Figure 4).

The left auricle and ventricle showed no abnormalities such as those found in the right heart. The thickness of the auricular wall was normal and the myocardium was not hypertrophied. The endocardium was translucent. In the left ventricle the myocardium appeared to be normal; the endocardium lining this chamber was smooth and of average thickness.

The papillary muscles were well formed and chordae tendinae reached to the margins of the two delicate mitral valve leaflets.

The coronary arteries, of particular interest in this case, were normal in every respect. Their orifices in the aorta were patent and in the usual position. The arteries followed normal courses over the surface of the heart, and the right ventricle received branches from the anterior descending branch of the left coronary artery as well as from the right coronary artery. There was nowhere evidence of coronary artery occlusion and all branches could be easily followed. The coronary sinus, which followed a normal course, was dilated and showed an unusually heavy wall.

The ductus arteriosus was obliterated and the ligamentum arteriosum was in the normal position. The heart measurements follow: tricuspid valve—4 cm., pulmonary valve—2 cm., mitral valve—2.2 cm., aortic valve—2 cm., right ventricle wall—1.5 mm., left ventricle wall—8 mm., right auricle—3 mm.

The left lung was atelectatic, the right lung contained air. The trachea and bronchial tree were normal. The liver was greatly enlarged, weighing 350 gm., and its cut surface presented a typical "nutmeg" appearance of chronic passive congestion. The gall bladder and bile ducts were normal. The spleen weighed 25 gm. The stomach, intestines and mesentery, except for rather marked edema, were normal. There were no abnormalities in any of the other viscera. The lymph nodes of the tracheo-bronchial, cervical, axillary, inguinal and retroperitoneal regions were not enlarged. The aorta was elastic and its intima smooth, with no coarctation. The epiphyseal line of the ribs appeared straight and the rib and vertebral marrow appeared normal. Permission for examination of the cranium was not obtained.

Microscopic Examination

Sections were taken from both the left and right heart. A section from the left heart shows a normal endocardium, myocardium and epicardium of the ventricle and auricle, as well as a normal mitral valve. The following sections were taken from the right heart: two of the anterior wall extending to the beginning of the pulmonary conus, two of the posterior ventricular wall including part of the auricle and tricuspid valve, and one across the septum on the anterior surface of the heart. All sections were stained with hematoxylin and eosin, Mallory's Azo-carmine, and Weigert or Verhoeff-van Gieson stains.

The section from the anterior wall of the heart, including septum and right ventricle, demonstrates clearly the defect in the myocardium: in the right ventricle wall epicardium and endocardium lie adjacent to each other with no intervening cardiac muscle (Figure 3). There is thickening of the endocardium in places with an increase of elastic and connective tissue. The epicardium is composed of connective tissue and a small amount of superficial fatty tissue with numerous coronary blood vessels running through it. The myocardium of the septum is normal, but at the junction of the septum with the right ventricle wall the myocardium ends abruptly. The endocardium lining the left ventricular surface of the septum is of normal thickness. A section from the apex of the right ventricle shows in the fibrous connective tissue between the thickened endocardium and epicardium small deposits of hemosiderin and of amorphous material (staining purple with hematoxylin) suggesting calcified debris which may be the result of an old hemorrhage.

Extreme chronic passive congestion characterizes the liver but is less obvious in the other organs, none of which shows any significant microscopic lesion.

DISCUSSION

The lesion in this heart is characterized by almost total absence of the myocardium from the apex to the base of the right ventricle, while no patho-

logic changes are found in the left heart, and the coronary arteries are normal. Endocardium and epicardium are contiguous. At the base of the ventricular chamber on the posterior surface there is cardiac muscle in the tricuspid valve ring and in the pulmonary conus. No chronic inflammatory cellular infiltrations are present, apart from the minimal reaction underlying the organizing thrombi.

In explaining the pathogenesis of this lesion, there are three possibilities to consider: 1) myocardial infarction with healing; 2) a defect from intrauterine destruction of the myocardium by an inflammatory or degenerative process; and, finally 3) a primary developmental defect.

It is possible that the lesion resulted from infarction of the myocardium. In the newborn and infant, coronary artery disease or anomalies of the coronary arteries associated with massive infarction of the myocardium have been reported (2–7); however, in this heart case, the coronary arteries have a normal size, distribution and patency. Furthermore, there is no demonstrable source for coronary emboli and no evidence of embolization of the left ventricle or other organs.

Farber and Hubbard (8) and Abbott (9) have reported instances of idiopathic fetal endomyocarditis in which valvular abnormalities accompanied focal myocardial scars; in none of the cases studied by these authors was there any massive defect of the myocardium, the characteristic lesion of this particular heart in which all valves are normal. In a premature infant dying shortly after birth, Diamond (10) has described total replacement of the myocardium of the right auricular appendage by scarring and calcification, as well as scattered focal lesions in the ventricular muscle. Froboese (11) has reported an infant six months old with rather widely disseminated, patchy fibrosis of the myocardium with normal valves. This lesion might well have resulted from post-partum myocardial damage. It is possible that the loss of myocardium in the present heart represents the result of extensive intrauterine destruction of the right ventricular myocardium, but careful study of the material leaves the writer with the impression that this explanation is not valid; there is no evidence of prior inflammatory disease producing the anomaly. The valves are completely normal, and endocardial thickening in places would be expected from prolonged ventricular dilatation with organizing mural thrombi. Thrombosis commonlyoccurs in dilated chambers without an inflammatory or necrotic basis. There is no trace of scarring between the endocardium and epicardium. The abrupt cessation of the myocardium at the junction of the septum and right ventricle wall with the clearly juxtaposed endocardium and epicardium (Figure 3) are particularly significant in ruling out a fetal degenerative or inflammatory process.

Finally, there is the possibility that this lesion represents a true primary congenital defect in the development of the heart. A developmental defect is

the only plausible explanation for the abnormality described in this heart. The basis for this explanation is laid in Davis' (1) observations on the early stages of the growth and development of the human heart. At the 4 somite stage the myocardium of the future heart consists of a bilaterally symmetrical mantle of mesenchymal cells enclosing an endothelial plexus. The mantle comprises a pair of cardiogenic folds, one of which forms the epicardium and myocardium of the right ventricle, the other those of the left ventricle. The endocardium and valves develop from the endothelial plexus. By the 9 somite stage complete fusion of the paired cardiogenic folds has occurred. Therefore, at the 4 somite stage in the human embryo, the future right and left myoepicardium exist as two separate primordia, to be completely fused as early as the 9 somite stage. Thus, injury to the right cardiogenic fold at this embryologic stage might result in the development of a heart without myocardium in the right ventricle. It can be concluded that since the endocardium and valves develop from the endothelial plexus, a defect in the cardiogenic fold would not lead to defective development of the valves or of the endocardium.

The pathologic findings in this infant indicate that the injury to the heart was long-standing, with no evidence of recent or acute changes in the myocardium. Thus it is altogether unlikely that a post-natal pathological process (apart from infarction, and the coronary arteries were normal and patent) would be limited to almost complete destruction of the right ventricle alone or would have produced a lesion such as that illustrated in Figure 3. Therefore, it is the writer's belief that the injury to the heart occurred during intrauterine life, and that the most likely cause of this anomaly was a primary congenital defect in the maturing embryo with abnormal formation and anomalous development of the primordium of the right ventricular myocardium. While cardiac muscle was present in the right ventricular wall, both at the base on the posterior aspect and in the pulmonary conus, a primary congenital defect need not, of course, be a total one. On examination of the gross and microscopic material, the late Dr. George L. Streeter, concurred in the opinion that this was a congenital anomaly resulting from a defective or injured right cardiogenic fold. Some theories on the development of the four chambers of the heart have assumed the presence of a functioning myocardium in the wall of each chamber. If one now assumes that a four-chambered human heart can so develop in the absence of the right myocardium, it may be necessary to reconsider previous ideas concerning the development of four heart chambers from a simple cardiac tube.

SUMMARY

A previously undescribed malformation of the heart is presented with a brief summary of the clinical history and a detailed account of the autopsy

findings. The basic defect is almost total absence of the myocardium of the right ventricular wall. The pathogenesis of the lesion is discussed. It is believed that this malformation probably represents a primary congenital defect in the maturing embryo with abnormal formation and anomalous development of the primordium of the right ventricular myocardium.

I wish to express my appreciation to Dr. Arnold R. Rich and to Dr. William Carnes for invaluable advice and criticism during the preparation of this paper.

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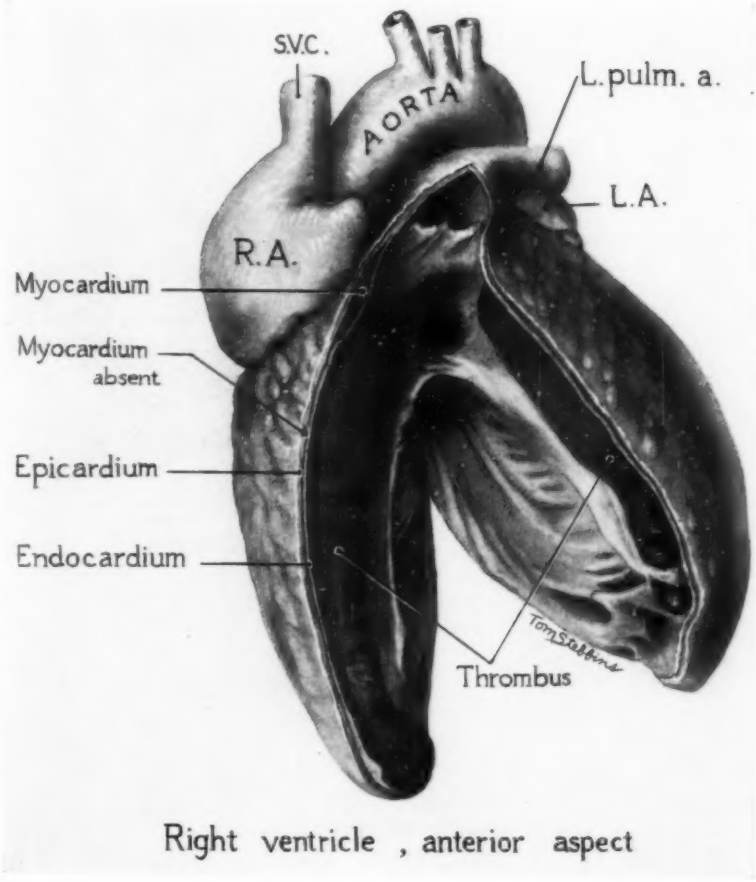
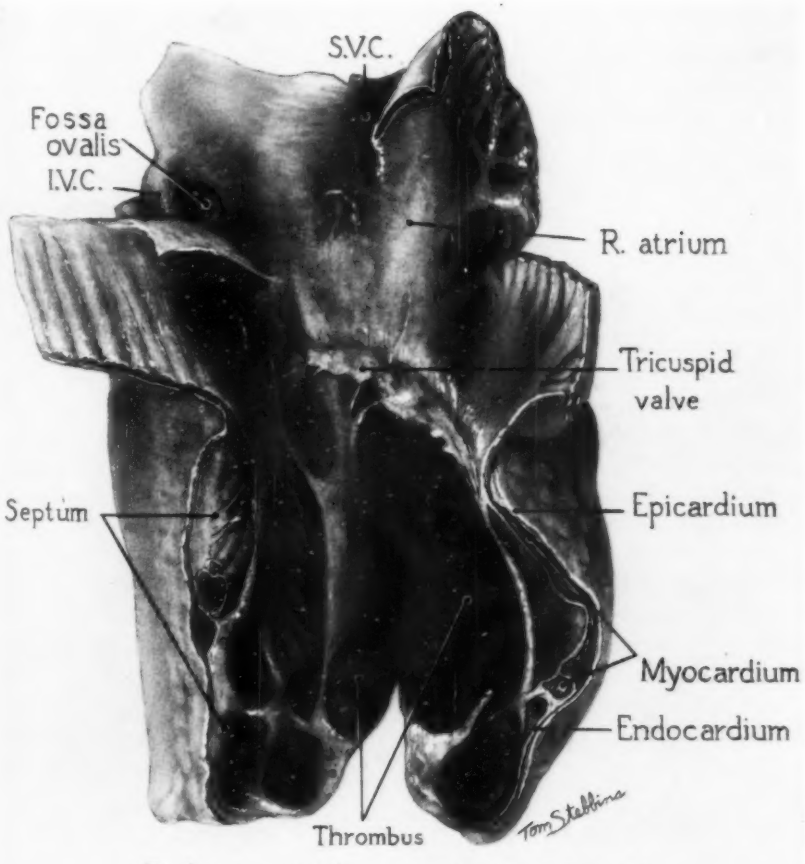
PLATE 1. Drawing of the heart from the anterior aspect, showing clearly the defect in the wall and the position of the thrombus.



Right ventricle, anterior aspect

PLATE 2. Drawing of the heart from the posterior aspect, demonstrating well the hypertrophied auricular wall, the delicate tricuspid valve leaflets and the isolated remnant of myocardium in the right ventricular wall.



Right ventricle, posterior aspect

THE ACTION OF NICOTINAMIDE AND ISONICOTINIC ACID HYDRAZIDE ON DIPHOSPHOPYRIDINE NUCLEOTIDASES

A Preliminary Note

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Because of the recent introduction of isonicotinic acid hydrazide as a chemotherapeutic agent in the treatment of tuberculosis, the following observations are thought to be of sufficient general interest for publication here in preliminary form.

The cleavage of diphosphopyridine nucleotide (DPN, ARPPRN[2]) at the nicotinamide-ribose linkage:

$$\text{ARPPRN} + \text{H}_2\text{O} \rightarrow \text{ARPPR} + \text{N}$$

by enzymes from animal tissues is known to be inhibited by nicotinamide (N) (1, 2, 3, 4). Recent studies (5) have shown that the cleavage of this linkage by an enzyme from *Neurospora crassa* is relatively unaffected by nicotinamide. The present work (6) was undertaken to investigate the basis for the difference in nicotinamide sensitivity betwen the animal and *Neurospora* enzymes.

A particulate enzyme preparation from beef spleen, purified by fractional centrifugation (7), was compared with a soluble enzyme preparation from *Neurospora*, purified as described previously (5). Studies of nicotinamide inhibition at varying DPN concentrations revealed that the inhibition was non-competitive with DPN in the case of the sensitive spleen enzyme, but competitive with DPN in the case of the relatively insensitive *Neurospora* enzyme. Inhibition of the spleen enzyme could be readily reversed by dialysis or dilution.

The non-competitive but reversible nature of the inhibition of the beef spleen enzyme by nicotinamide, taken together with the irreversible nature of the over-all reaction, as indicated by lack of enzymatic synthesis of ARPPRN from ARPPR plus N (2, 5), led to the development of the following hypothesis for the mode of action of the enzyme (E):

$$\text{ARPPRN} + \text{E} \underset{\text{(a)}}{\rightleftharpoons} \text{ARPPR—E} + \text{N}$$

$$\text{ARPPR—E} \xrightarrow[\text{(b)}]{\text{H}_2\text{O}} \text{ARPPR} + \text{E}$$

[1] Contribution No. 29, of the McCollum-Pratt Institute. Aided by grants from the American Cancer Society, as recommended by the Committee on Growth of the National Research Council, the Williams-Waterman Fund, and the Rockefeller Foundation.

[2] The symbol ARPPRN represents the diphosphopyridine nucleotide structure: adenine-ribose-phosphate-phosphate-ribose-nicotinamide.

According to this hypothesis, added nicotinamide would inhibit the spleen enzyme by competing with H_2O for the ARPPR-E complex, thereby driving reaction (a) to the left.

In order to test this hypothesis, nicotinamide labeled with C^{14} in the carboxamide group was incubated with unlabeled DPN and the spleen enzyme at nicotinamide concentrations which prevented DPN breakdown. Under appropriate conditions it was found that an exchange reaction occurred, resulting in com-

TABLE I

Action of Nicotinamide and Isonicotinic Acid Hydrazide on Mammalian Diphosphopyridine Nucleotidases

The tissues were homogenized in 0.1 M phosphate pH 7.5; 0.1 ml. of 1:10 brain homogenate or 1:50 spleen homogenate was incubated with 0.8 μM DPN, varying amounts of inhibitor, and 0.05 M phosphate buffer, pH 7.5, in a volume of 0.6 ml., for 8 minutes at 37°. DPN was measured spectrophotometrically by means of alcohol dehydrogenase (9). Values expressed as per cent inhibition.

	NICOTINAMIDE (M)			ISONICOTINIC ACID HYDRAZIDE (M)		
	7.5×10^{-4}	2.5×10^{-3}	2.5×10^{-2}	7.5×10^{-4}	2.5×10^{-3}	2.5×10^{-2}
Beef brain	25	68	98	92	92	—
Beef spleen	22	44	89	68	78	84
Lamb brain	30	76	81	94	96	100
Lamb spleen	16	65	78	62	73	81
Rat brain	9	41	92	5	9	13
Rat spleen	20	43	82	0	11	50
Mouse spleen	27	66	100	0	0	0
Mouse lymphoma	56	66	100	0	0	0
Rabbit brain	18	39	70	3	9	34
Rabbit spleen	16	37	74	8	22	44

plete equilibration of the unlabeled nicotinamide in the DPN with labeled nicotinamide:

$$\text{ARPPRN} + \overset{*}{\text{N}} \rightleftharpoons \text{ARPPR}\overset{*}{\text{N}} + \text{N}$$

These results support the above hypothesis for the mode of action of nicotinamide on the spleen enzyme. If the *Neurospora* enzyme is inhibited by a different mechanism, involving simple competition with DPN at high nicotinamide concentrations, as has been described for certain dehydrogenase systems (8), no incorporation of labeled nicotinamide into DPN would be expected with this enzyme. This has indeed been found to be the case; no significant incorporation could be detected even at very high nicotinamide concentrations.

McIlwain (4) has shown that a number of compounds structurally related to nicotinamide can act as inhibitors of the DPN-splitting enzyme in brain. From the results reported here, the possibility arises that compounds of this type may act by actually replacing the nicotinamide moiety of the DPN molecule. This would result in the formation of analogs of DPN which, in all likelihood, would

behave differently from the parent compound in certain DPN-requiring systems. In view of the structural similarity between nicotinamide and isonicotinic acid hydrazide, it appeared possible that the antibiotic activity of the latter compound might result from a reaction of the type described above.

Preliminary studies of isonicotinic acid hydrazide have shown that it is approximately ten times as effective as nicotinamide in inhibiting the beef spleen enzyme. A concentration of 1.3×10^{-4} M was sufficient to cause 50 per cent inhibition under the conditions used. The similarity to nicotinamide is further emphasized by the failure of the hydrazide to inhibit the *Neurospora* enzyme appreciably, even at a concentration of 0.1 M. Isonicotinic acid, like nicotinic acid, has no effect on either enzyme.

A surprising species specificity for the effect of the hydrazide has also been noted (Table I). Whereas the enzyme in the brain or spleen of beef or lamb is extremely sensitive to the hydrazide, the enzyme in the corresponding tissues of the rat, mouse and rabbit is relatively insensitive, showing little or no inhibition at concentrations as high as 10^{-2} M. In contrast, sensitivity to nicotinamide is essentially the same in all species.

It has also been found that isonicotinic hydrazide will inhibit the incorporation of labelled nicotinamide into DPN by the beef brain enzyme, but has no effect on the incorporation in the rat brain system. This further suggests a difference in response to the compound by the various species.

The mode of action of the hydrazide on DPNases is being further pursued, and details of this investigation will be published elsewhere.

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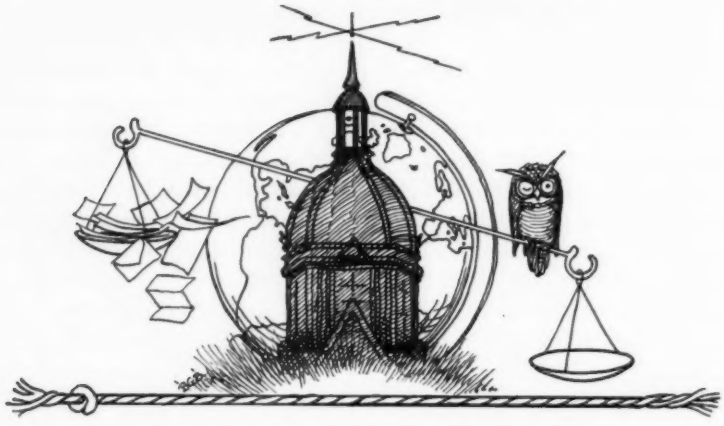

BOOK REVIEWS

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Callander's Surgical Anatomy, 3rd edition. By BARRY J. ANSON AND WALTER G. MADDOCK. 1074 pp., $14.00. *W. B. Saunders Co., Philadelphia, Pa.*

In 1932 Dr. C. Latimer Callander, Associate Professor of Surgery and Topographic Anatomy at the University of California Medical School, published the first edition of his *Surgical Anatomy*. In a foreword of this book, Dr. Dean Lewis wrote, "We have long been in need of a book in which anatomy and its surgical application are considered together or in close sequence. . . . The book's appearance should be eminently satisfying."

Heretofore, such efforts had amounted to little more than handbooks of anatomy in abbreviated form with a faint tinge of surgical application, of which Davis' *Applied Anatomy* was probably the most ambitious one published in this country. Callander's book met with immediate success. The contents were listed under ten main chapters, The Head, Neck, Thorax, Abdomen, Pelvis, Male Perineum and External Genitalia, Female Perineum and External Genitalia, The Vertebral Column, Upper Extremity, and Lower Extremity. The book was revised by Dr. Callander in 1939.

In 1950 there appeared the *Atlas of Human Anatomy* by Dr. Barry J. Anson, Professor of Anatomy at Northwestern University Medical School. This magnificent book represents an atlas of gross anatomy whose pictorial content is based upon new dissections, serially prepared and upon variable morphological features statistically present. This work served and still serves as a continuously useful reference to the reader based, not upon perennially copied figures, but upon the artists' unbiased portrayal of dissections. It is pure anatomy, no references being made to surgery.

In 1952, Dr. Anson, the anatomist, and Dr. Walter Maddock, the Professor of Surgery at Northwestern University, combined their fields in order to write the third edition of Dr. Callander's Surgical Anatomy. The result is a very happy one. Two dozen of the splendid drawings from the Atlas are great additions to the text. Fortunately, fundamental features of anatomy, not detailed surgical technique, are stressed. One criticism which seems warranted is that the text, and particularly the illustrations, of the portion dealing

with the brain are not commensurate with those dealing with the other portions of the body. The addition of a few illustrations showing the fundamental surgical approaches to lesions of the brain, such as those in Dandy's chapter on the Brain in the Lewis *System of Surgery*, would add much to the value of this part of the book.

I. R. T.

Textbook of Medicine, 10th edition. Edited by SIR JOHN CONYBEARE AND W. N. MANN. 912 pp., $8.00. *The Williams & Wilkins Co., Baltimore, Md.*

This is the tenth edition of a textbook of medicine widely used by medical students throughout the British Empire. Since the previous edition, the sections on Infectious Fevers and Tropical and Helminthic Diseases have been rewritten by new contributors. New sections on congenital heart disease and anticoagulant drugs have been added.

The purpose of this book is to "provide within as small a compass and as low a price as possible the essentials of medicine." In 895 pages this is a difficult task, particularly when sections on skin and childhood diseases are included. The discussion of diseases of the nervous system by F. M. R. Walshe offers in 162 pages a clear and concise summary of the subject which is sufficiently detailed for reference. Unfortunately, other sections, although presenting essentials, are in some cases too brief to answer many of the questions which arise in the day to day care of patients.

This book is written by a group of distinguished clinicians, and laboratory techniques, except for electrocardiography, are not emphasized. Space also prevents a full integration of some of the newer physiological concepts into an understanding of disease and its treatment. A bibliography would allow students to round out and supplement some of the important points which a book on essentials of medicine does not cover.

The purpose of this book is brevity. Long experience with repeated editions has allowed the editors to distill essentials from the muddy ferment of medical knowledge. Some readers will find that favorite ingredients have been omitted, but the overall purpose of presenting essentials has been accomplished.

D. C.

A Textbook of Pharmacology. Principles and Application of Pharmacology to the Practice of Medicine. By WILLIAM T. SALTER. 1240 pp., $15.00. *W. B. Saunders Co., Philadelphia, Pa.*

It is difficult to understand what prompts a scientist to write a large tome covering some major sphere of medical activity. The complete mastery of such branches of medical science as physiology, biochemistry, and pharmacology is impossible for most mortals today. Yet not infrequently a hardy soul takes pen (and reputation) in hand in an attempt to provide a comprehensive and up-to-date survey of an entire field for the medical student and practitioner. The latest entry in the literary sweepstakes is Professor Salter of Yale, who has written what purports to be a textbook of pharmacology representing the standpoint of the clinician as well as the pharmacologist. Sad to relate, Dr Salter has come a cropper from both standpoints, with unfortunate results.

Some aspects of the book are merely annoying, such as the many pages devoted to large reproductions of plant sources of drugs, the inconstant policy in regard to typesetting when the text is interrupted by diagrams, tables, or pictures, the listing and description of drugs which are neither of theoretical nor practical significance, etc. Other faults, however, are less forgiveable. A reader has the right to expect lucid, orderly presentation of material; many sections are jumbled, repetitious, difficult to follow, and liberally sprinkled with *non sequiturs*. There are a surprising number of errors of fact. Thus one reads

that "sulfonamides may be injected into, or irrigated through the spinal canal," that morphine may be given to an "exhausted" asthmatic, that most cardiac aglycones are combined with glucose (and not pentoses) to form the simple glycosides, that sulfanilamide is a "simple homolog of acetanalid," that strychnine is "often" used in the treatment of acute barbiturate poisoning. Most pharmacologists and clinicians do not recommend quinidine as an antidote for digitalis poisoning; Dr. Salter's story of the patient who was treated for the latter condition with 30 grams of quinidine in one day "with recovery" inspires respect for the ability of the human body to withstand insult rather than for the wisdom of the treatment. Careful rereading of the text by the author would have eliminated such boners as: the effect of "nitroglycerin under the tongue . . . will last for forty minutes" in the text and "4–8 minutes" in a table on the same page, or the "cautious increase" in quinidine dosage from 1 gram a day for a few days to "0.6 gram distributed over the course of a day," or the description of the "8 cc. needle . . . inserted to a depth of 5 cc."

Disturbing too are such omissions as the basic principles underlying the absorption, transport, and distribution of the volatile anesthetics, Butler's work on the fate of chloral hydrate in the discussion of the Meyer-Overton theory, the work of Strauss and coworkers on the mechanism of alcohol diuresis, the work of Brodie *et al.* on the fate of thiopental, the reports on the anesthesia produced by the rare inert gases, the effects of n-allyl normorphine in the chapter on morphine.

The book is adequate in parts, but it is written so unevenly and sloppily that it cannot be recommended as a text or reference book. To make things worse, it is both unwieldy and expensive. Dr. Salter has obviously spent a good deal of time and effort in compiling this opus. It is unfortunate that the final outcome could not have been more sanguine.

L. L.

Surgery and the Endocrine System. By JAMES D. HARDY. 153 pp., $5.00. *W. B. Saunders Co., Philadelphia, Pa.*

In this monograph Hardy's first objective has been "to outline the mechanisms by which the patient survives injury, and to attempt to clarify for the general surgeon ways in which certain recent advances in physiology affect surgical care." In abbreviated form, he discusses the endocrine physiology of the alarm reaction, fluid balance, nutrition and early ambulation. The endocrinology of surgical infections, thermal burns, tissue repair and neoplasia is considered briefly. The second half of the book contains a more detailed description of surgery of endocrine glands: the thyroid, parathyroids, pancreas, adrenals, pituitary, thymus and gonads. These sections include illustrations of technique, as well as notes on pre-, and post-operative management.

For brevity in discussing such extensive topics as these, the author has had to limit each chapter to those facts and theories most generally acceptable today. Several chapters are so brief that only the accompanying bibliography will be of value to the reader. Some excellent original work has been included but the monograph is primarily a compendium.

P. L. B.

Living in Balance. By FRANK S. CAPRIO. 246 pp., $3.75. *The Arundel Press, Washington, D. C.*

This is another in an ever increasing number of volumes devoted to the cookbook approach to psychiatry. As the chapters unfold, the reader is introduced to one after another ingredient of personality which, if mixed or unmixed according to direction, should lead to "Living in Balance." Situations of all varieties are analyzed and an appropriate, pre-

packaged cake mix solution designed to assure success is presented. Some of these are implemented by case histories and a guide to dream analysis is offered in the interest of hastening the acquisition of a better product. Somehow by following the author's recipe and presumably without requiring any box tops to be torn off better mental health is to be achieved.

In the same sense that most would frown on the publishing of popular books designed to teach the lay reader the performance of self-surgery, psychotherapy so presented has dangerous potentialities. To a large degree the illness of those patients with which the author is concerned consists of not being able to do the very things he exhorts them to do. Only increased frustration and heightened morbid preoccupation can result from such advice, perhaps with more severe illness ensuing. The individual in borderline adjustment may find this state more difficult to maintain due to seizing upon any of the wide variety of pseudo-therapeutic vignettes reported. The normal individual probably will take away an extremely oversimplified, artificial, and distorted view of what psychiatry is, one that would be unsympathetic to its practitioners and to its patients as well.

L. H. G.

Refraction and Mobility. By WALTER B. LANCASTER. 432 pp., $7.75. *Charles C Thomas, Springfield, Illinois.*

This fine book is based on the author's 35 years of teaching experience. It successfully bridges the gap between the theoretical optics of the physicist and those practical aspects of the science used daily by the refractionist. The subject is presented from the point of view of the vergence of light rays avoiding all Gaussian theorems. Although the careful avoidance of mathematical formulae necessitates considerable elaboration and circumlocution, it is most welcome to those of us not mathematically inclined. An excellent and detailed description of the practical methods of measurement of refractive errors makes this a most useful book for the ophthalmologist. Great emphasis is placed on subjective methods, of which the author was an ardent advocate. Motility problems and their measurements are also discussed. The set of 50 problems and their answers in the appendix should prove of great value for those preparing for examinations.

B. B.

BOOKS RECEIVED FOR REVIEW

Annual Review of Medicine. Edited by W. C. CUTTING AND H. W. NEWMAN. Editorial Committee: J. S. L. BROWNE, A. M. BUTLER, K. S. GRIMSON, E. M. MACKAY AND S. C. MADDEN. 442 pp , $6.00 *Annual Reviews Inc., Stanford, California.*

Ansprachen. By WALTER STOECKEL. 133 pp., Kart. DM 7.80. *Georg Thieme Verlag, Stuttgart, Germany.*

Correlative Cardiology: An Integration of Cardiac Function and the Management of Cardiac Disease. By CARL E. SHAFFER AND DON W. CHAPMAN. 525 pp., $9.50. *W. B. Saunders Co., Philadelphia, Pa.*

Diseases of the Nervous System, 7th edition. By F. M. R. WALSHE. 365 pp., $5.50. *The Williams & Wilkins Co., Baltimore, Md.*

Dynamic Aspects of Biochemistry, 2nd edition. By ERNEST BALDWIN. 544 pp., $5.00. *Cambridge University Press, New York.*

Essentials of Public Health, 2nd edition. By WILLIAM P. SHEPARD. With the Collabora-

tion of CHARLES EDWARD SMITH, RODNEY RAU BEARD AND LEON BENEDICT REYNOLDS. With a Foreword by RAY LYMAN WILBUR. 581 pp., $6.50. *J. B. Lippincott Co., Philadelphia, Pa.*

Lehrbuch der Inneren Medizin, Vol. I. Edited by HELMUT DENNIG. 972 pp., Vol. II, 1060 pp., each volume Ganzl. DM 41. *Georg Thieme Verlag, Stuttgart, Germany.*

Living Agents of Disease. By JAMES T. CULBERTSON AND M. CORDELIA COWAN. 624 pp., $5.50. *G. P. Putnam's Sons, New York.*

The Origin of Life and the Evolution of Living Things. An Environmental Theory. By OLAN R. HYNDMAN. 648 pp., $8.75. *The Philosophical Library, New York.*

The Principles and Methods of Physical Diagnosis. Correlation of Physical Signs with Physiologic and Pathologic Changes in Disease. By SIMON S. LEOPOLD. With a Chapter on **Sounds from the Thorax: Acoustic Principles** by S. REID WARREN, Jr. 430 pp., $7.50. *W. B. Saunders Co., Philadelphia, Pa.*

Psychiatry and Medical Education. Report of the 1951 Conference on Psychiatric Education held at Cornell University, Ithaca, New York, June 21–27, 1951. Organized and conducted by the American Psychiatric Association and the Association of American Medical Colleges. Editorial Board: JOHN C. WHITEHORN, *Chairman*, CARLYLE JACOBSEN, MAURICE LEVINE AND VERNON LIPPARD. 164 pp., $1.00. *American Psychiatric Association, Washington, D. C.*

Symposium on Radiobiology. The Basic Aspects of Radiation Effects on Living Systems. Oberlin College, June 14–18–, 1950. Edited by JAMES J. NICKSON. Editorial Committee; P. MORRISON, M. BURTON, E. S. GUZMAN BARRON, G. FAILLA AND H. M. PATT. Sponsored by The National Research Council of the National Academy of Sciences 465 pp., $7.50. *John Wiley & Sons, New York.*